Respiratory Management Following Spinal Cord Injury

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Key Points

1.1 Evidence of Pharmaceutical Interventions

The use of bronchodilators should be considered in people with tetraplegia who demonstrate an element of obstructive airway impairment.

The effects of other medications commonly used in the management of SCI, such as baclofen and oxybutynin, should be considered when reviewing airway hyperreactivity in people with tetraplegia.

The short-term use of oxandrolone can be considered to improve pulmonary function in people with tetraplegia.

1.2 Evidence of Mechanical Ventilation (MV) and Weaning Protocols

Progressive ventilator free breathing (PVFB) protocol should be considered for ventilator dependent people with tetraplegia who are appropriate for ventilator weaning.

Resistive and endurance training should be considered in people who are candidates for ventilator weaning.

1.3 Evidence of Tracheostomy (TOT) Decannulation

There is some evidence that the implementation of an invasive acute phase respiratory management for patients with cervical SCI receiving tracheostomy (TOT) or endotracheal intubation provides successful in TOT removal.

There is some evidence that a specific protocol; which consists of decannulating patients whose assisted peak cough flow (APCF) without an external control device substituting for glottic function was <160L/min and their APCF with the device was measured as ≥160L/min; is beneficial for determining TOT decannulation in patient s with neuromuscular diseases, including patients with SCI.

Until more evidence is available, case by case consideration should be given to TOT decannulation in people with SCI. The indications and criteria for TOT decannulation have not yet been well established in SCI.

1.4 Evidence of Exercise Training of the Upper and Lower Limbs

For exercise training to improve respiratory function the training intensity must be relatively high (70-80% of maximum heart rate) and performed three times per week for six weeks.

Ideal training regimes have not been identified.

1.5 Evidence of Respiratory Muscle Training

Respiratory muscle training (RMT) (including IMT, IMT + EMT, and different combinations of other breathing training exercises) generally improves respiratory muscle strength and endurance, pulmonary function, and functionality in people with SCI.

Dosage of RMT should be defined as there are multiple types, duration, and protocols that have been tested in the literature.

1.6 Evidence of Assistive Devices and Other Treatments

Abdominal binding (AB) can be used to achieve immediate improvements in respiratory function, but long-term effects can be sustained during its application.

Chest wall vibration may improve pulmonary function while the vibration is applied, but carry-over effects when the vibration is not in use have not been evaluated.

There is limited evidence that immersion to shoulder-deep 33-34° C water can improve pulmonary function immediately, but carry-over effects following immersion have not been evaluated.

1.7 Evidence of Sleep Disordered Breathing (SDB)

Patients with SCI have a high prevalence of obstructive sleep apnea (OSA), and therapy may improve quality of life (QOL) and other outcomes. Therefore, we recommend vigilance for suggestive signs and symptoms (e.g., snoring, obesity, witnessed apneas, daytime sleepiness) and further testing in patients with suggestive symptoms/signs (with overnight oximetry or polysomnography [PSG]).

1.8 Evidence of Cough Assist and Secretion Removal

There is limited evidence that suggests that improving inspiratory and expiratory muscle force is important to maximize expiratory flow during cough.

Cough effectiveness can be enhanced by a variety of methods including manual assistance by a caregiver, RMT, glossopharyngeal breathing (GPB), spinal cord

stimulation (SCS), and/or electrical stimulation (ES) triggered by the person with SCI.

Hand-held expiratory pressure devices may enhance secretion removal in people with SCI.

Lung volume recruitment (or “breathstacking”) including mechanical insufflation-exsufflation (MIE) coupled with chest wall therapy has been shown to improve peak cough flow (PCF) and respiratory system compliance.

1.9 Evidence of Electrical Stimulation (ES)

There is some evidence that suggests a higher survival rate in phrenic paced participants compared to mechanically ventilated participants.

Phrenic nerve or diaphragmatic stimulation may be used as a long-term alternative to MV for people with injuries at C2 or above.

Diaphragm pacing system (DPS) can help patients with SCI to breathe without a mechanical ventilator, specifically at long term follow-up; with the period of acclimatation recommended to be individualized and gradually incremented, particularly in those patients who have been mechanically ventilated for long periods.

There is some evidence that restoration of diaphragm innervation through nerve transfer (using intercostal or inferior laryngeal nerve) into the phrenic nerve is feasible and successful in reinnervation of the diaphragm in patients with SCI, but the evidence regarding achieving ventilator independence is still contradictory.

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1 Executive Summary

1.1 What Respiratory Problems Occur After Injury?

- **Difficulty clearing mucus**: The airways naturally produce mucus to trap debris. Problems with coughing or swallowing can cause the mucus to collect in the airways. This can encourage the growth of bacteria.
- **Pulmonary embolism:** When a blood clot forms, it can travel and cause a blockage within the lungs. This is referred to as pulmonary embolism.
- **Reduced lung capacity:** If the respiratory muscles are weak or paralyzed, not as much air can be breathed into or out of the lungs.
- **Respiratory failure:** When the lungs cannot efficiently exchange carbon dioxide for oxygen, oxygen levels may become too low or carbon dioxide levels may become too high.
- **Pneumonia:** When bacteria or viruses find their way into the lungs, an infection known as pneumonia can occur.

Respiratory system complications can be made worse by pre-existing medical conditions, history of smoking, advanced age and by therapeutic measures to manage the resuscitation phase of the injured patient.

1.2 How Common are Respiratory Problems After Spinal Cord Injury?

Respiratory problems are common, affecting 36-83% of people with spinal cord injury (SCI) in their acute phase or early phase of injury. Pneumonia, collapsed lung, and respiratory failure are the three most common respiratory problems. Respiratory complications continue to be one of the leading causes of morbidity and mortality in people with SCI, especially among cervical and higher thoracic injuries.

The complexity and the severity of respiratory problems after SCI depend on which respiratory muscles are affected and at what level the SCI is. Complete paralysis of all muscles involved with respiration occurs when the lesion is above C3; this type of injury requires immediate and permanent ventilatory support in order to sustain life. When the injury is between C3 to C5 (innervation of the diaphragm), respiratory insufficiency occurs via respiratory muscle dysfunction.

SCI at most levels affects innervation of the abdominal muscles which severely compromises the ability to generate cough and clear respiratory secretions. Cough generation is accomplished by a large inspiratory volume followed by an expulsive expiration produced by the expiratory intercostals muscles (thoracic roots) and the abdominal muscles (T4-L1). Cough is important as a defense mechanism to prevent respiratory tract infections (RTI) and atelectasis, a complete or partial collapse of the entire lung or area (lobe) of the lung. The respiratory system has other important roles such as speaking and posture-related activities which can also be negatively impacted by the SCI, especially with higher lesions.

1.3 What are the Risk Factors for Respiratory Problems?

Many factors may contribute to how respiratory problems develop. These include:

- Completeness of the injury.
- Cause of the injury.
- Problems from tracheostomies or mechanical ventilation (MV).
- A more severe injury.
- A larger lesion.
- A higher level of injury.
- Other fractures.
- A surgical tracheostomy (TOT) instead of a percutaneous TOT.
- No return of certain reflexes one day after the SCI.

1.4 What Management Options are There for Respiratory Problems?

Non-pharmacological Options

- There is evidence from a case series study that progressive ventilator free breathing (PFVB) protocol is more successful for weaning people with C3 and C4 spinal cord injuries than intermittent mandatory ventilation (IMV).
- Resistance and endurance training might improve resting and exercising respiratory function and should be considered in people who are candidates for ventilator weaning.
- The indications and criteria for TOT tube removal have not been definitively established in SCI.
- For exercise training of the upper and lower limbs to improve respiratory function the training intensity must be relatively high (70-80% of maximum heart rate) performed three times per week for six weeks. Whereas ideal training regimes have not been identified.
- Respiratory muscle training improves respiratory muscle strength and endurance in people with SCI. Two RCTs and several case control and pre-post studies support RMT (IMT + EMT) as an intervention that will improve inspiratory and expiratory muscle strength, pulmonary function and functionality an exercise capacity. Five RCTs and several pre-post and case studies support inspiratory muscle training (IMT) as an intervention that will improve inspiratory muscle strength and might decrease dyspnea and respiratory infections (RI) in some people with SCI. Three RCTs and several case control and pre-post studies support other protocols such as music, vocal intonation rehabilitation, and other combinations of breathing training exercise as an effective way to improve pulmonary function, functionality, and quality of life (QOL) in patients with SCI.

- Abdominal binding (AB) in people with tetraplegia can improve respiratory function, and longer-term use can continue to be effective.
- Chest percussion is a method where vibrations to the chest loosen mucus for easier removal. Vibrations can be made by clapping the chest. During manual assisted coughing, gentle pressure is applied to the chest during coughing. These techniques have been shown to reduce deaths related to respiratory problems. Chest wall vibration may improve pulmonary function while the vibration is applied (level 4 evidence based on one pre-post study) but long-term effects when the vibration is not in use has not been evaluated.
- Patients with SCI have a high prevalence of obstructive sleep apnea (OSA), and therapy may improve QOL and other outcomes. Therefore, we recommend vigilance for suggestive signs and symptoms (e.g., snoring, obesity, witnessed apneas, daytime sleepiness) and further testing in patients with suggestive symptoms/signs (with overnight oximetry or polysomnography [PSG]).
- Secretion removal techniques are common practice in people with SCI and yet there is predominantly only level 4 evidence to support the use of some airway clearance techniques to facilitate secretion removal in this population. There is level 2 evidence in support of mechanical insufflation/exsufflation (MIE) coupled with manual chest therapy kinesitherapy techniques.
- Cough effectiveness can be enhanced by a variety of methods including manual assistance by a caregiver, respiratory muscle training (RMT), glossopharyngeal breathing (GPB), spinal cord stimulation (SCS), and/or electrical stimulation (ES) triggered by the person with SCI.
- Phrenic nerve or diaphragmatic stimulation may be used as a long-term alternative to MV for people with injuries at C2 or above, and that people in phrenic paced conditions have lower mortality than their mechanically ventilated counterparts. Long-term partial or total independence from MV can generally be interpreted as a successful intervention with these devices.
- There is no evidence that we know of that supports one airway clearance technique over another, and there are no criteria available to indicate when to implement the various airway clearance techniques.

Pharmacological Options

- The use of Bronchodilators should be considered in people with tetraplegia who demonstrate an element of obstructive airway impairment. For instance, one RCT showed that salmeterol had beneficial effect on respiratory function in people with tetraplegia; bronchodilators may also have additional effects in strengthening breathing muscles such as the diaphragm. Caution should be used with ipratropium as it has been proposed that it may cause mucus in the airways to thicken, neutralizing its positive effects on breathing, though some studies have shown positive effects of ipratropium and metaproterenol on pulmonary function in people with tetraplegia.

- The effects of medications commonly used in the management of SCI, such as baclofen and oxybutynin, can decrease or block hyperresponsiveness to methacholine, but not histamine, in tetraplegia. There is one RCT that showed that high dose IV ambroxol after surgery increases blood oxygenation in patient with cervical SCI and motor complete injuries.
- There is conflicting evidence that the short-term use of oxandrolone improves pulmonary function in people with tetraplegia.

1.5 Limitations of What We Know

Much of the SCI respiratory literature focuses on the acute care of the patient with SCI. Given that long-term survival rates following SCI have increased in recent years, a greater understanding of the effects of chronic SCI on the respiratory system is necessary. This is largely because there have been relatively few well-designed studies that point to effective management strategies. Specific major concerns include an overall lack of RCTs; small patient sample sizes that offer little statistical power; lack of appropriate control or placebo groups; and inadequate characterization of the SCI. In addition, most studies do not consider gender, time since injury, smoking history, and other respiratory complications. As such, the amount and quality of the literature can be considered modest at best and the ability to generalize is limited.

If we determined the most efficient and effective techniques that are comfortable and readily adhered to for people with SCI in order to facilitate airway clearance, it would improve their QOL and decrease health care.

1.6 For More Information

SCIRE Professional: Pulmonary Complications During Acute SCI. Available from https://scireproject.com/evidence/respiratory-management-acute-phase/methods/

Clinical practice guidelines addressing SCI: The Paralyzed Veterans of America (PVA) Consortium for Spinal Cord Medicine—Respiratory management following spinal cord injury: a clinical practice guideline for health-care professionals (2005).

2 Methods

A literature search was performed using the following databases: Cochrane Library, PubMed/MEDLINE, EMBASE, CINAHL, and Scopus. The following search terms were entered: (spinal cord injury OR paraplegia OR quadriplegia OR tetraplegia OR spinal cord impaired OR spinal cord lesion) AND acapello, airway, airway pressure, apnea, asthma, atelectasis, barotraumas, breathing, bronchial lavage, bronchitis, bronchoscopy, cardiopulmonary function, cardiorespiratory, COPD, cough, diaphragm, dysphagia, expiration, exsufflation, flutter, Garshick, inspiratory, insufflations, lung, percussion, phrenic nerve, pneumonia, positive airway pressure, pulmonary, pulmonary capacity, pulmonary complications, pulmonary embolism, pulmonary health, pulmonary secretions, respiration, respiratory capacity, respiratory complications, respiratory endurance, respiratory function, respiratory health,

respiratory muscle, respiratory secretions, sleep apnea, smoking, spirometry, steroid respiratory, tidal volume, ventilation, ventilator weaning, ventilatory capacity, ventilatory failure, abdominal binder, assisted cough, autogenic drainage, BiPAP, breathing exercises, chest physiotherapy, cough, CPAP, diaphragmatic pacemaker, expiratory pressure device, exsufflation, futter device, flutter valve, forced expiratory technique, glossopharyngeal breathing, incentive spirometry, insufflations, intermittent positive pressure breathing, intrapulmonary percussive ventilation, IPPB stretch, manual percussion, manual vibration, mechanical vibration, paripep, PEEP, PEP, percussion, phrenic pacemaker, positive pressure breathing, postural drainage, progressive ventilatory free breathing, respiratory exercise, respiratory training, secretion removal, spirometry, synchronous intermittent mandatory ventilation, TheraPep, tracheostomy, ventilation, ventilator, or ventilator weaning. Each search term after the brackets was added separately.

The following limits to the search were applied: the article must have been published between January 1, 1990 and December 31, 2021 in English, and included humans over the age of 18 years. The search was restricted to journal articles, reviews, and systematic reviews; grey literature, conference abstracts, case reports, study protocols, and qualitative studies were excluded. The studies had to include a minimum of three patients, of which ≥50% had spinal cord injuries, unless the results stratified injury etiology. During this process, additional studies were added as a result of cross-referencing between studies. Efforts were made to focus on the most recent studies and the highest levels of evidence available.

3 Introduction

“Despite significant progress in both basic and clinical research, there is still a significant gap in our understanding of the effect of SCI on the respiratory system” (Zimmer et al. 2007, p. 319). The respiratory system, including the lungs, respiratory muscles, and neural control system, is a complex integrated physiological system that is not yet fully understood. The respiratory system is unique in that it must operate in a cyclical and highly coordinated fashion for 24 hours per day to sustain life. Respiratory complications are one of the leading causes of morbidity and mortality in people with spinal cord injury (SCI), especially among cervical and higher thoracic injuries (Rabadi et al. 2013; Cao et al. 2013; Shavelle et al. 2006). This continues to be the case despite recent advances in SCI patient care where acute and long-term mortality rates have been significantly reduced (Cao et al. 2013). Respiratory system complications can be exacerbated by pre-existing medical conditions, history of smoking, advanced age, and by therapeutic measures to manage the resuscitation phase of the injured patient.

Respiratory dysfunction resulting from cervical SCI depends on the level of injury and the extent of innervation. The higher-level lesions result in denervation of progressively more of the expiratory and inspiratory muscles as illustrated in Figure 1. Although the primary consequence of SCI is denervation of the respiratory pump, secondary consequences occur within the lungs because of the inability to effectively distend and inflate the lung to its full capacity. As a consequence, the compliance of the lungs diminishes with increasing time after SCI.

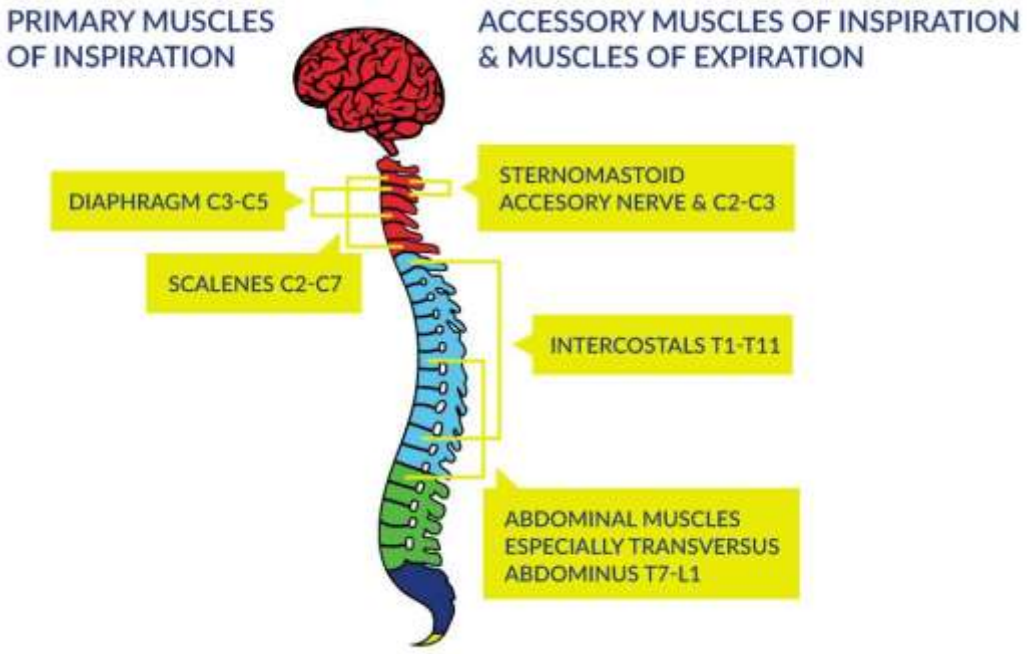


Figure 1. Innervation of the Respiratory Muscles

Complete paralysis of all muscles involved with respiration occurs when the lesion is above C3; this type of injury requires immediate and sometimes permanent ventilatory support to ensure arterial blood gas homeostasis and to sustain life. When the injury is between C3 to C5 (innervation of the diaphragm), respiratory insufficiency occurs via respiratory muscle dysfunction. Although primary and some accessory muscles of inspiration are fully innervated with injuries below cervical levels, the ability to ventilate at higher levels is still compromised because the intercostals and other chest wall muscles do not provide the integrated expansion of the upper chest wall as the diaphragm descends during inspiration. Furthermore, ventilation during exercise can be greatly compromised. The expiratory muscles actively contract in without SCI whereas partial or fully denervated expiratory muscles in those with SCI will diminish exercise ventilation and ventilatory reserve.

Lung volumes reflect these diminished capacities for full inspiration and forced expiration in people with SCI. These pulmonary function measures are derived by having the person breathe normally followed by full inspiration and full expiration in and out of an apparatus that measures lung volumes (Figure 2). As expected, lung volumes like the inspiratory capacity (IC) and expiratory reserve volume (ERV), are progressively smaller in higher cervical lesions vs. lower thoracic and lumbar lesions (Baydur et al. 2001).

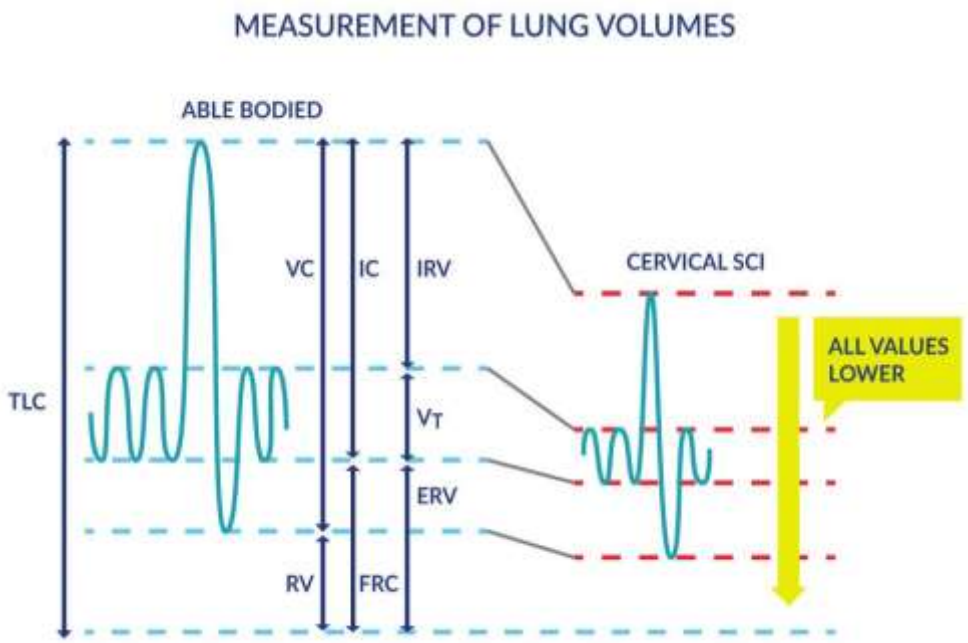


Figure 2. Measurement of Lung Volumes

Lung Volumes	*Lung Capacities*
Tidal volume (V_T but also known as TV): Volume of air inhaled or exhaled during breathing (at rest or during exercise). **Inspiratory reserve volume (IRV):** Maximum volume of air that can be inhaled to total lung capacity (TLC) over and above the V_T. **Expiratory reserve volume (ERV):** Maximum volume of air that can be exhaled from the end-expiratory level or from functional residual capacity (FRC) to residual volume (RV). **Residual volume (RV):** Volume of air remaining in the lungs after a maximal expiration.	**Inspiratory capacity (IC):** Maximal volume of air that can be inhaled (sum of V_T and IRV). **Functional residual capacity (FRC):** Volume of air remaining in the lungs at the end of an ordinary expiration, i.e., at the resting level or end-expiratory level. **Vital Capacity (VC):** Maximum volume of air that can be expelled after a maximum inspiration, i.e., from total lung capacity (TLC) to residual volume (RV). **Total Lung Capacity (TLC):** Total amount of air in the lungs after a maximal inspiration. TLC = RV + ERV + V_T (TV) + IRV.

The forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are usually measured to detect airways obstruction. Due to reduced inspiratory muscle force, these measures are diminished in people after SCI with higher lesions and especially in people with tetraplegia (Linn et al. 2000; Baydur et al. 2001) and demonstrate moderate correlation with injury level (Baydur et al. 2001). Longer duration of injury and smoking are two factors

associated with greater loss while incomplete lesions (compared to complete lesions) have lesser degrees of compromise of forced expiratory measures of FEV_1 and FVC (Linn et al. 2000).

SCI at most levels affects innervation of the abdominal muscles (Figure 1), which severely compromises the ability to generate cough and clear respiratory secretions. Cough generation is accomplished by a large inspiratory volume followed by an expulsive expiration produced by the expiratory intercostals muscles (thoracic roots) and the abdominal muscles (T4-L1). Cough is important as a defense mechanism to prevent respiratory tract infections (RTI) and partial or total lung collapse. The respiratory system has other important roles such as speaking and posture-related activities which can also be negatively impacted by the SCI, especially with higher lesions.

In summary, the respiratory consequences of SCI are common and are largely dependent on the level of injury. Additional large-scale cross sectional and longitudinal studies are required to fully characterize pulmonary function in SCI. Secondary respiratory complications related to other respiratory pathologies (i.e., chronic obstructive pulmonary disease [COPD], asthma) are not well described. In particular, the consequences of aging on pulmonary function are not well defined in SCI. With healthy aging there is a decline in lung function, primarily because of a loss of elastic recoil. Moreover, additional age-related changes that are known to negatively affect gas exchange are decreased surface area of the lung, decreased pulmonary capillary blood volume, increased dead space ventilation, and decreased distensibility of the pulmonary arterial vasculature. A greater understanding of the interactions between SCI, aging and the respiratory system are necessary for comprehensive patient management.

While it is clear that the respiratory system can be compromised with SCI, the salient question is: *what intervention strategies are known to be effective for patient management?* The subsequent sections are divided into commonly used respiratory-related interventions used for the respiratory management of the patient with SCI.

4 Predictors for Respiratory Function in SCI

There are several predictors (factors/injury level) of respiratory function in patients with SCI which should be considered:

- **A lower lesion level positively predicts lung function and respiratory muscle strength in people with motor complete SCI** (Mueller et al. 2012; N=440). Mueller et al (2008; N=109) reported a significantly lower lung function in patients with SCI and high tetraplegia (C3-C5), compared with low tetraplegia (C6-C8), and low tetraplegia compared with low paraplegia patients (T7-T12).
- **Younger age, being male, heavier, and tall were also significant positive predictors of lung function parameters** (Mueller et al. 2012; **N=440).** Inspiratory muscle strength (PI_{max}) was positively predicted by younger age, being male, and being heavier, while expiratory muscle strength (PE_{max}) was positively predicted from younger age, being male, and a greater time since injury.
- **Wheezing significantly predicted (after adjusting for age) mortality in patients with chronic SCI, with a relative risk of 2.38** (Garshick et al. 2005; N=361). A persistent wheeze (after

adjusting for age) marginally predicted mortality, with a relative risk of 1.87 (Garshick et al. 2005; N=361).

- Garshick et al. (2005; N=361) **reported a 3% decrease in mortality rate with every increase in percent-predicted FEV_1 and FVC.**
- **Patients with SCI with a higher lesion level (C1-C5) and injury severity (ASIA A) are at greater risk of mortality (odds ratio of 2.3, p = 0.0002) than ventilator-dependent patients with SCI with a lower level and severity (Shavelle et al. 2006; n=319).**
- Shavelle et al. (2006; N=1986) also suggested that following discharge, **patients with SCI and with lower-level injuries (C6 below) are more likely to wean off ventilator dependency, compared to higher and more severe SCI injuries (i.e., C1-C5 ASIA A).**
- A Swedish retrospective study found the **risk of mortality (relative risk) to be 2.1 times greater in patients with SCI who experienced respiratory complications during their first rehabilitation visit,** compared with those who had no respiratory complications (Josefson et al. 2021; N=136).
- The risk of pulmonary complications was 10 times more likely in AIS A patients and 1.7 times more likely in AIS C patients compared with AIS D (Aarabi et al. 2012, n=109).

The effects of respiratory function on functional outcomes are listed below:

- Patients with SCI and **dyspnea during physical activity and rest (p < 0.001), weak cough strength (p = 0.02), and a reduced FVC (p = 0.04) reported significantly greater restrictions in social functioning** (Postma et al. 2016; N=147).
- Phrenic nerve stimulation (PNS), in comparison with mechanical ventilation (MV), is suggested to significantly (p < 0.001) improve quality of speech in respiratory device-dependent patients with SCI (Hirschfeld et al. 2008; N=64). Although a small sample size, patients with SCI on PNS were more likely to return to work or school, compared with the MV group (Work, PNS 7 vs. MV 2; School, PNS 2 vs. MV 0) (Hirschfeld et al. 2008; N=64).
- In the presence of respiratory complications, patients with SCI are less likely to participate in 18 of 26 different daily activities (Cobb et al. 2014; N=1137). **Specifically, there was a 20% to 139% increased probability that patients with SCI would be less likely to participate as much as they wanted in a specific daily activity.** The relative risk of not participating in traveling and holidays was 1.20, while the relative risk of not communicating by electronic means was 2.39 (Cobb et al. 2014; N=1137).
- **Patients with SCI who did not require ventilator use at discharge report a better quality of life (QOL) and health status 1 year following injury, compared to those who required assisted ventilation (Charlifue et al. 2011; N=1635).** In the 1635 patients with SCI assessed, the non-ventilator group reported a better health status than the previous year (odds ratio 1.2, p = 0.012), and a reduced depression incidence (OR 1.7, p = 0.045) compared with the ventilator group (Charlifue et al. 2011; N=1635). Satisfaction with life was reported to be 1.7 times greater in the non-ventilator group compared with the ventilation group (p = 0.015). Although social integration had a reported odds ratio of 1.65, it was not a significant predictor in the model (Charlifue et al. 2011; N=1635).

- A multicenter study of 14 trauma centers in the USA found approximately 72% of people with SCI at discharge did not require MV (Kornblith et al. 2013; N=360). In the cervical SCI subgroup analysis, approximately 84% had successful extubation, and 62% were discharged not requiring MV.
- Kornblith et al. (2013; N=360) also reported that participants with SCI and with a cervical injury were 14 times more likely to continue with MV following tracheostomy (TOT) ($p < 0.05$).
- Sports injuries, a higher AIS admission score, lesion length, younger age, and a greater neurological level were associated with pulmonary complications (Aarabi et al. 2012; n = 109).

Table 1. Respiratory Predictors: Large Correlational/Cross-sectional Studies on Level of Injury/Function

Author Year Study Design	Population Characteristics	Methods	Outcomes
Aarabi et al. 2012 USA Case series Level 4 N = 109	**N:** 109 **Level:** C2-C4: 47 C5-T1: 40 T2-T12: 14 L1-S1: 8 **AISA Impairment Scale Grade:** A: 48 B: 16 C: 13 D: 32 **Etiology:** Motor vehicle accidents, falls, sports and other. **Mean Age (SD):** 42.76 ± 16.7 **Median Time since Injury (IQR):** ± **Female:** n=23	**Study Duration:** 2005 – 2009 **Outcome Measures:** Pulmonary complications. **Objectives:** Define and analyze the predictors of moderate and severe pulmonary complications following SCI and investigate whether pulmonary complications negatively affected the ASIA Impairment Scale conversion rate in patients with SCI.	1. Eighty-seven pulmonary complications occurred in 51 patients. a. Twenty-six patients had ventilatory failure. b. Twenty-five had pneumonia. c. Seventeen had pleural effusion. d. Six had acute lung injury. e. Four had pneumothorax. f. Four had lobar collapse. g. Pulmonary embolus and hemothorax were each encountered in 2 patients, and 1 patient had a mucus plug. 2. Patients with sports injuries and those between the ages of 26 and 35 years were particularly prone to pulmonary complications and had an RR of 1.65 and 1.73, respectively ($p = 0.04$). Individuals with ASIA motor scores less than 25 were almost 9 times more at risk of pulmonary complications than those with an ASIA motor score more than 50 (RR 8.7, $p < 0.0001$). Similarly, patients with ASIA Impairment Scale Grade A scores had more pulmonary complications (RR 8.2, $p < 0.0001$). Patients with complete SCI were 3

Author Year Study Design	Population Characteristics	Methods	Outcomes
			times more prone to pulmonary complications than patients with incomplete injuries (RR 3.36, p < 0.0001). As the single neurological level of injury ascended from S-1 to C-2, the rate of pulmonary complications increased concordantly. 3. The degree of maximum canal compromise in the spinal canal and maximum spinal cord compression did not influence the occurrence of pulmonary complications. However, as the length of intramedullary lesion on T2-weighted MRI studies exceeded 40 mm, the risk of pulmonary complications also increased by a factor of 2 (p = 0.004). 4. Patients with pulmonary complications had significantly longer LOSs (40.7 vs. 12.8 days, p = 0.05). 5. The overall rate of conversion in patients with moderate or severe pulmonary complications was 37.2%, similar to 31% in patients without moderate or severe pulmonary complications. 6. Controlling for age, mechanism of injury, neurological level, and length of intramedullary lesion, only the admission ASIA Impairment Scale grade predicted moderate or severe pulmonary complications; patients with increasing severity of ASIA Impairment Scale grade had a markedly increased risk. Patients with Grade A were nearly 10 times as likely, those with Grade B were 2.6 times as likely, and those with Grade C were 1.7 times as likely to have a moderate or severe pulmonary complication compared with those with Grade D.

Author Year Study Design	Population Characteristics	Methods	Outcomes
Josefson et al. 2021 Sweden Case series Level 4 N = 136	**N:** 136 **Level:** Cervical: 83 Thoracic-sacral: 53 C1-C4 AIS ABC: 22 C5-C8 AIS ABC: 23 T1-S5 AIS ABC: 34 AIS D: 44 **Etiology:** traumatic (84%): fall (33%) Non-traumatic: infection (5%) or vascular (5%) **Median Age (IQR):** 51 (33-65) **Median Time since Injury (IQR):** **Female:** 22%	**Study Duration:** Admitted between Jan 2010 and Dec 2014. Follow up on mortality ended 2018 **Outcome Measures:** AIS and Charlson Comorbidity index, Breathing aid defined as (non-invasive ventilation [NIV]; CPAP [continuous positive airway pressure]; Bi-level PAP, BiPAP), tracheostomy (TOT), use of cough assist machine, ICD codes **Objectives:** To determine prevalence of respiratory complications in people with SCI during the initial rehabilitation at the spinal cord injury unit (SCU) and to describe the subsequent effect on mortality.	1. 38% required some breathing aid during their initial rehabilitation period in the SCU 2. 40% had acute respiratory complications during their stay in the SCU. Pneumonia was diagnosed in 35% 3. More than half of the participants with cervical SCI (n = 43) had respiratory complications during their initial rehabilitation in the SCU, and 20% (n = 11) of participants with lower injuries experienced the same 4. Of the 23% deceased at follow-up, respiratory causes contributed to one-third of the deaths (n = 10). 5. The RR of dying if the person suffered from any respiratory complications during their initial rehabilitation in the SCU was 2.1 times higher than for those with no respiratory complications (RR, 2.10; 95% CI, 1.1–3.9). While a history of pneumonia was associated with 72% higher mortality, this was not statistically significant (RR, 1.72; 95% CI, 0.9–3.2). 6. A history of respiratory complications in the SCU was associated with a higher mortality and a tendency of a shorter life span ($p > 0.05$) 7. Of the 10 who died from respiratory causes, 8 suffered from pneumonia during their initial rehab in the SCU and had a 4.3 times higher risk (RR, 4.27; 95% CI, 1.1–16.9) of dying from respiratory causes later compared to those who did not suffer from pneumonia at the SCU. 8. 6 of 10 participants required use of the cough assist machine during their stay in the SCU, which also indicated a significantly higher risk

Author Year Study Design	Population Characteristics	Methods	Outcomes
			of death due to respiratory causes (RR, 3.15; 95% CI, 1.1–8.7).
Mueller et al. 2008 Netherlands (8 SCI rehab centers) Prospective cohort study Level 2 N = 109	**N:** 109 **Level:** Acute, motor complete SCI (ASIA A or B) included **Etiology:** **Mean Age (SD):** 38 +- 14 **Median Time since Injury (IQR):** **Female:** n=28 *Subgroups: High tetraplegia (HT [C3-C5]) Low tetraplegia (LT [C6- C8]) High paraplegia (HP [T1-T6]) Low paraplegia (LP [T7- T12])	**Study Duration:** Between Aug 2000 and July 2003. Assessments at first mobilization, discharge and 1 year after discharge **Outcome Measures:** 1. Lung function (FVC, FEV_1, FIV_1, PEF, PIF) 2. Respiratory muscle pressure generating capacity (PI_{max}, PE_{max}) **Objectives:** To investigate the time-courses of lung function and respiratory muscle pressure generating capacity after SCI.	**Longitudinal changes:** 1. FVC and FEV_1 increased in all four groups until one year after discharge from inpatient rehabilitation. 2. FIV_1, PEF and PIF generally remained constant during the first year after discharge. 3. PI_{max} showed significant increases during and after inpatient rehabilitation, while PE_{max} showed significant increases only in participants with paraplegia during inpatient rehabilitation. **Influence of lesion** 1. HT showed significantly lower FVC, FEV_1, FIV_1 and PEF values than LT while these values were significantly higher for LP than LT. 2. There were no significant differences between LT and HP in any of the tested lung function parameters. 3. PE_{max}, PI_{max} and P_{endu} were lower in participants with tetraplegia compared to participants with paraplegia. 4. PE_{max} of participants with tetraplegia did not change over time, PE_{max} of participants with paraplegia increased during inpatient rehabilitation but decreased thereafter. **Influence of personal factors** 1. Personal factors such as gender, age and height had significant influences on all lung function parameters, except age had no influence on PEF (PEF seems not to decrease with age).

Author Year Study Design	Population Characteristics	Methods	Outcomes
			2. Body mass and smoking had no significant effect on any of the measured parameters. 3. PI_{max} and PE_{max} were only influenced by gender which resulted in higher estimates for men than for women.
Shavelle et al. 2006 USA Retrospective (25 SCI centres) Level 4 N = 810	**N:** 810 people, 319 first year survivor (SCI who are ventilator dependent at discharge) **Level:** ASIA A: 74 ASIA B: 13 ASIA C: 8 ASIA D/unknown: 6 **Etiology:** Fall (n=22), MVA (40), sports (15), violence (13), other (10) **Age (n):** 20-49: 74 50-79: 26 80+: 0 **Median Time since Injury (IQR):** **Female:** 18%	**Study Duration:** 1986 person years occurring from 1973 to 2003. Patients with SCI from inpatient rehab who survive at least 1 year after injury. **Outcome Measures:** Mortality, cause of death, neurologic level of injury **Objectives:** Identify factors related to long-term survival, and quantify their effect on mortality and life expectancy	1. Even in a population limited to ventilator-dependent persons, those with the most severe injury grade (ASIA A) had poorer survival. 2. The C1-C5 ASIA A group was at 2.268 (OR) times greater odds of dying than among ventilator-dependent persons who were not C1-C5 ASIA A (p=0.0002). 3. C1-C5 ASIA B injuries had a significantly better prognosis than C1-C5 ASIA A (OR = 0.45, P < 0.05), and C5 was similar to C1-C4. Our impression was that many persons with injuries at levels C6 and lower are eventually weaned from ventilator dependence after discharge, whereas comparatively fewer of the C1-C5 ASIA A persons are subsequently weaned. 4. Life expectancy among the ventilator-dependent persons decreases both with age and severity of injury. For example, the life expectancy is 18.6 years for a 30-year-old who has a C1-C5 ASIA A injury but only 2.2 years for an 80 year old. 5. Cause of death was known for 84 of 121 cases (69%). Pneumonia and other respiratory diseases were the main cause of death 26 (31 %).
Postma et al. 2016 Netherlands	**N:** 147 **Level:** Motor complete (AIS A and B)	**Study Duration:** 5 year follow up of prospective cohort study. Admission to rehab was	1. 30.9% of all people had impaired FVC (below 80% of the predicted value), 35.9% perceived poor or moderate cough strength and 18.4% (at rest) and 29.0% (during activity)

Author Year Study Design	Population Characteristics	Methods	Outcomes
Follow-up of prospective cohort (8 rehab centers) Level 2 N = 147	tetraplegia: 33 Incomplete (AIS C and D) tetraplegia: 21 Motor complete (AIS A and B) paraplegia: 67 Incomplete (AIS C and D) paraplegia: 26 **Etiology:** Traumatic (78.9%) **Mean Age (SD):** 45.5 (13.8) **Mean Time since Injury (SD):** 6.6 (0.8) yr **Female:** 28.6%	between Aug 2000 and July 2003 **Outcome Measures:** 1. Pulmonary function (FVC) 2. Respiratory function (self-report cough strength and dyspnea) 3. HRQOL (sickness impact profile 68 [SIPSOC] and SF-36) 4. Respiratory infections (RI) **Objectives:** Examine the prevalence of impaired respiratory function (objective pulmonary and perceived respiratory function), the incidence of RI and the associations among these parameters in people with SCI 5 years after initial inpatient rehab. Secondly, assess the associations between respiratory function and HRQOL (expressed as: social functioning, general health, mental health, and vitality).	experienced dyspnea (occasionally, regularly, or often). 2. When corrected for the lesion level and completeness, people with lower FVC (p=0.04), poor perceived cough strength (p=0.02) and more dyspnea at rest and during physical activity (p<0.001) reported more limitations in social functioning (SIPSOC). 3. People with dyspnea at rest reported lower general health (occasional dyspnea, p=0.03; regular, p=0.02) mental health (regular dyspnea, p=0.04) and vitality (regular, p=0.08). General health was lower in those with regular dyspnea than in occasional dyspnea at rest (beta-coefficient, -12.1 vs. -27.6, respectively). 4. People with dyspnea during physical activity reported lower general health (occasional dyspnea, p=0.02; regular, p=0.04) mental health (occasional dyspnea, p=0.01; regular dyspnea, p=0.03) and vitality (occasional dyspnea, p=0.01; regular, p=0.05). General health, mental health and vitality range were lower in those with regular dyspnea than in occasional dyspnea.
Mueller et al. 2012 Netherlands (8 centers) and Switzerland (9 SCI centers) Cohort Level 2	**N:** 440 **Level:** Motor complete AIS A or B with lesion level C4-T12 included **Etiology:** Traumatic **Median Age:** 47 (21-72)	**Study Duration:** **Outcome Measures:** 1. Lung function (FVC, FEV_1, PEF) 2. Respiratory muscle strength tests (Peak inspiratory and expiratory muscle strength [PI_{max}, PE_{max}]) **Objectives:** To develop statistical models to predict lung	**Revised summary:** A lower lesion level positively predicts lung function and respiratory muscle strength in participants with motor complete SCI. Younger age, being male, heavier, and tall were also significant positive predictors of lung function parameters. PI_{max} was positively predicted by younger age, being male, and being heavier, while PE_{max} was positively predicted from younger age, being male, and a greater time since injury.

Author Year Study Design	Population Characteristics	Methods	Outcomes
N = 440	**Median Time since Injury:** 15.7 (0.7-40.9) yr **Female:** n=89	function and respiratory muscle strength from personal and lesion characteristics of participants with motor complete SCI.	1. Group means of FVC, FEV_1 and PEF values increased with lower lesion level, but showed a large range between participants of the same group. 2. Multivariate analysis - all lung function parameters are significantly associated with the level of injury ($p<0.05$) but showed a large range between participants of the same group. Individuals with lower lesion levels showed higher values than participants with higher lesion levels. Men showed significantly higher values than women, younger participants showed higher values than older ones, taller and heavier participants showed higher values than smaller and lighter ones. Time post injury and the interaction of lesion level and age had no significant influence on any of the tested lung function parameters. R2 for FVC was 0.55, for FEV_1 0.52 and for PEF 0.40. 3. Group means of PI_{max} and PE_{max} increased with lower lesion level, but also showed a large range between participants of the same group. Participants with lower lesion levels showed higher values than those with higher lesion levels, and men showed higher values than women. Increasing age had a negative influence on PI_{max} and PE_{max}, whereas greater body mass was positively associated with PI_{max} but not with PE_{max}. Height and time post injury had no significant influence on PI_{max}. PE_{max} was positively associated with time post injury. The total variance of the models that can be explained by included factors (R2), was 0.37 for PE_{max} and 0.46 for PE_{max}.

Author Year Study Design	Population Characteristics	Methods	Outcomes
Garshick et al. 2005 USA Prospective cohort study Level 2 N = 361	**N:** 361 males **Level (survivors):** *Incomplete* Cervical ASIA C 35: Cervical ASIA D: 40 Other ASIA C: 25 Other ASIA D: 32 *Complete* Cervical: 69 High thoracic (T1–T4): 48 Low thoracic (T5–T12): 40 Others: 35 **Etiology:** Non-traumatic (6.5%) - infection (n=5), disc disease or spinal stenosis (3), tumor (4), six occurred following an unspecified operation, other cause (4) **Mean Age (SD):** 50.6 +- 15.0 at entry **Mean Time since Injury:** 17.5 +- 12.8 yrs at entry **Female:** 0	**Study Duration:** Between 1994 and 2000. SCI males >= 1-year post-injury. Participants were followed for a median of 55.6 months (interquartile range 42.0–67.5 months; range 0.33–74.4 months) **Outcome Measures:** 1. Health questionnaire 2. Pulmonary function (FEV_1, FVC, MEP, MIP) 3. National death index **Objectives:** To assess the relationship between comorbid medical conditions and other health related factors to mortality in chronic spinal cord injury (SCI).	1. Respiratory system deaths accounted for only 5.4% of the underlying causes of death. 2. Specific underlying and contributing respiratory deaths included pneumonia (n = 4), chronic airways obstruction (n = 3), pleural effusion (n = 1), and unspecified respiratory complications (n = 1). 3. After adjusting for age, any wheeze was a significant predictor (RR 1.54 unadjusted, 2.38 adjusted) and persistent wheeze was a borderline predictor (RR 2.06 unadjusted, 1.87 adjusted) of mortality. 4. After adjusting for age, percent-predicted FEV_1 (RR 0.97) and percent-predicted FVC (0.97) were related to mortality. Age-adjusted models for FEV_1 and FVC indicated that for each percent predicted increase in lung function, mortality decreased by 3%. 5. In the 348 participants with pulmonary function data available, significant predictors of mortality included age, percent predicted FEV_1 (RR 0.97), cigarette smoking (current cigarette consumption and smoking ≤ 7 years before study entry), diabetes, and heart disease.

Author Year Study Design	Population Characteristics	Methods	Outcomes
Cobb et al. 2014 Canada Cross-sectional Level 5 N = 1137	**N:** 1137 **Level**: 50.3% (95% CI 47-53) paraplegia, 49.7% (95% CI 47-53) tetraplegia, 39.1% (95% CI 36-42) complete, 60.9% (95% CI 58-64) incomplete **Etiology:** traumatic **Age:** 48.3 ± 13.3 years **Duration:** 18.4 ± 16.3 years **% Female:** 29.1% (95% CI 27-32)	**Timeline:** May 2011-Aug 2012 **Outcomes:** Two instruments, the SCI Health Questionnaire: Secondary Complications (SCI-HQ) and the person-perceived Participation in Daily Activities Questionnaire (PDAQ), that were originally created for the Rick Hansen SCI Registry Community Follow-Up Questionnaire V2.0. **Objective:** describe the association between secondary health complications and the ability to participate in daily activities among SCI people.	1. RI were associated with 18 daily activities. With all secondary health outcomes included, the RR values ranged from 1.15 to 2.53; this was a 15% to 153% increased probability of not participating as much as wanted in a particular DA, when a specific SHC is present.
Hirschfeld et al. 2008 Germany Prospective cohort Level 2 N = 64	**N:** 64 (32 PNS, 32 MV) **Level:** AIS A: 57 AIS B: 2 AIS C: 5 C0: 8 C2: 47 C3: 9 **Etiology:** **Median Age (range):** PNS: 29 (9-71) MV: 53 (6-77) **Time since Injury:** **Female:** n=18	**Study Duration:** Prospective data collection of treatment-related data over 20 years. Patients treated from 1987 through 2006. All patients were screened for check-up once a year **Outcome Measures:** 1. RI 2. Quality of speech 3. Presocial conditions 4. LoS **Objectives:** To compare MV with PNS for treatment of respiratory device-	1. Duration of rehabilitation was equal for patients on PNS (249 (7–1303) days) and patients on MV (290 (4–582) days). 2. Total 12 patients on PNS and 14 on MV died during the observation period (P = 0.1023); of these, 3 with PNS and 10 with MV died of RI (P = 0.0472). 3. Regarding RI, there is no significant difference between groups in period 1. However, during both 'post implantation' periods, 2 and 3, there are significantly fewer RIs with PNS than with MV (p<0.001). 4. There is no difference between PNS and MV for the ability to talk. The quality of speech is significantly better with PNS, where the lowest score was 3 (6 (5.25–6)), than with

Author Year Study Design	Population Characteristics	Methods	Outcomes
		dependent patients with SCI	MV, where speech scores were frequently 1 and 2 (3.5 (2–5.75)) (P<0.001). 5. Seven patients on PNS and two on MV returned to School or High School, two patients on PNS but none on MV returned to work and all others retired.
Kornblith et al. 2013 USA Case series Level 4 N = 344	**N:** 344 **Level:** Cervical injury: 222 (64.5%) Thoracic injury: 90 (26.2%) Lumbar injury: 32 (9.3%) Complete injury: 172 (20.0%) **Etiology:** **Median Age (range):** 43 (18-90) **Time since Injury:** **Female:** 19.5%	**Study Duration:** 14 trauma centers from 2005–2009 were evaluated **Outcome Measures:** Primary outcome: Need for MV at discharge. Secondary outcomes: Use of TOT, acute lung injury, and ventilator-associated pneumonia based on consensus definitions **Objectives:** Performed a multicenter cohort study to examine the predictors of ventilator dependence at discharge in patients with acute SCI	1. The majority (71.8%) did not require MV at the time of discharge. 2. The overall cohort had a high rate of VAP (38.1%), and patients with cervical SCI had significantly higher rates of ventilator-associated pneumonia than those with thoracic or lumbar injuries (cervical 45.1%, thoracic 32.2%, lumbar 6.3%, p<0.05). 3. Over half of the patients with high cervical SCI were off the ventilator at discharge (53.3%) 4. A higher percentage of patients were on MV at discharge in the TOT group compared to those who never underwent a TOT (85.6% vs. 53.7%, p<0.05). 5. As expected, patients requiring MV at discharge had significantly higher rates of ventilator-associated pneumonia (77.8% vs. 28.7%, p<0.05) and acute lung injury (17.5% vs. 4.9%, p<0.05), and longer ICU (25 vs. 10 days, p<0.05) and hospital stays (28 vs. 19 days, p<0.05). 6. In the cervical SCI cohort, we found TOT to be associated with 14.1-fold higher odds of prolonged MV (OR 14.1, CI 2.78–71.67, p<0.05).

5 Systematic Reviews

Ten systematic reviews have examined various interventions that affect respiratory function and management of people with SCI. Interventions examined include respiratory muscle training (RMT), abdominal binding (AB), secretion removal techniques, exercise training, and treatments for acute SCI and sleep disorders. These systematic reviews are outlined in Table 1 below, however, the conclusions and recommendations related to these findings are incorporated in the specific sections later in the module that summarize the respective treatments.

Table 2. Systematic Reviews

Author Year Country Date included in the review Number of articles Level of evidence Type of study AMSTAR Score	Methods Databases	Conclusions
Schreiber et al. 2021 Canada Reviewed published articles up to August 2021 N = 39 **Level of evidence:** Newcastle–Ottawa Scale **Type of study:** N/A AMSTAR: 6	**Methods:** Investigate the probability of weaning success, duration of MV, mortality, and their predictors in mechanically ventilated adult patients with SCI. **Database:** OVID Medline, CINAHL, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, Ovid Embase and Scopus.	1. A total of 14,637 patients were enrolled (13,763 in ICU, 874 in rehabilitation units). The mean time from injury to hospitalization was 8 h [95% CI 7–9] for studies conducted in ICU, 40 days [95% CI 29–51] for studies performed in rehabilitative units. 2. Probability of weaning from MV after SCI: a. 63% [45–78%] of the patients hospitalized in ICU were completely separated from the ventilator; 72% [51–86%] of the patients admitted to a rehabilitative ward were completely, and 82% [70–90%] were either completely or partially liberated from the ventilator. Figure 1. 3. Secondary outcomes: a. In ICU, the mean duration of MV was 27 days, LOS 23 days, hospital LOS 44 days. 81% of patients were tracheostomized and 30% of them were decannulated. Incidence of pneumonia and mortality were 40% and 8%, respectively. Figures 2 and 3. b. Patients hospitalized in rehabilitation centres were ventilated for a mean of 97 days (including duration of MV prior to admission and during the stay in rehabilitation) and stayed in the unit

for 78 days. All patients were tracheostomized and 83% of them were decannulated; 36% developed pneumonia, and less than 1% died. Figures 2 and 3.

4. Predictors of weaning and duration of MV:
   a. A high number of comorbidities, high Injury Severity Score, high-level lesions (C1–C3 vs. C4–C7), elevated heart rate, and presence of TOT appeared to be associated with increased odds of weaning failure.
   b. Shorter time to admission to a specialized SCI center, high-level lesions (C1–C4 vs. C5–C8), complete lesion, low V_T and high positive end-expiratory pressure within 24 h from admission, and presence of TOT were associated to a longer duration of MV.

Figure 1. Forest plots for the outcome of complete liberation from the ventilator (left panel) and for the outcome of partial or complete weaning after rehabilitation (right panel). Studies are presented according to setting classification (intensive care units vs. rehabilitation units): both overall and subgroup estimates are reported.

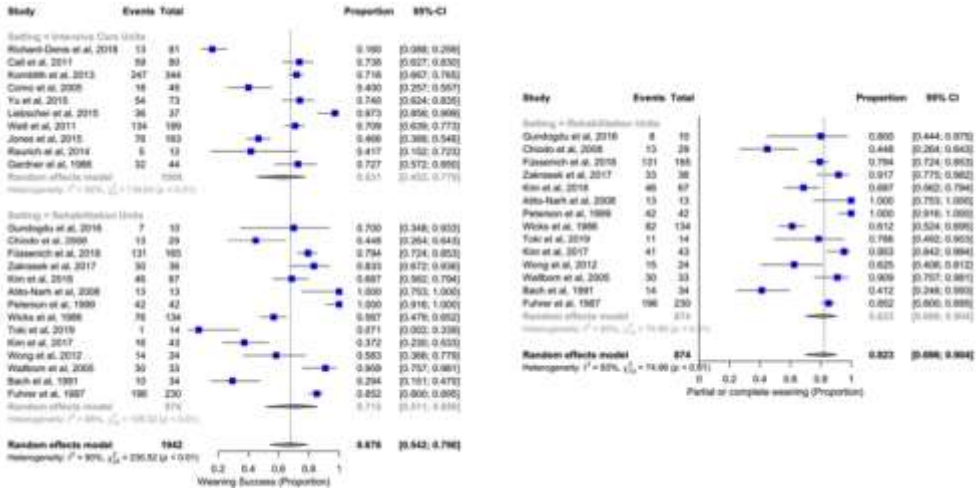


Figure 2. Forest plot for the outcome of duration of MV in intensive care units and rehabilitation units (upper panel). Studies
are presented according to setting classification (intensive care units vs. rehabilitation units): both overall and subgroup estimates are reported. Forest plots for the outcome of duration of MV for rehabilitation units (including the time to admission to rehabilitation) (lower panels). Weight refers to the relative contribution of each study to the meta-analytic estimate and is generated using the inverse variance method.

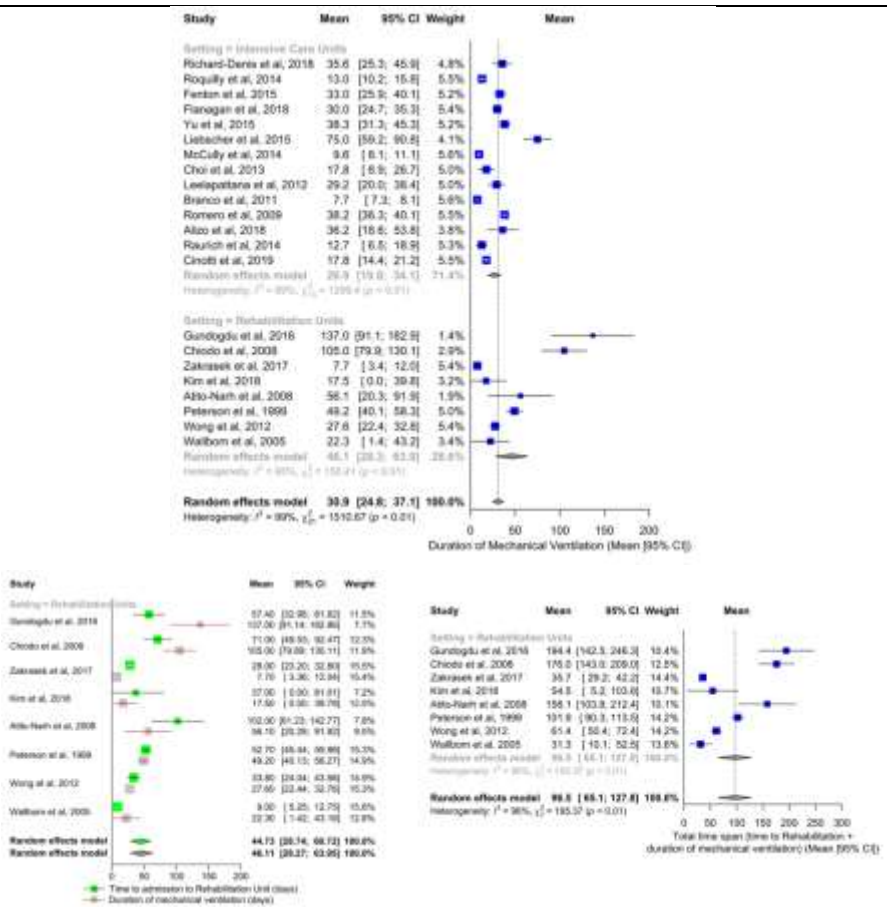
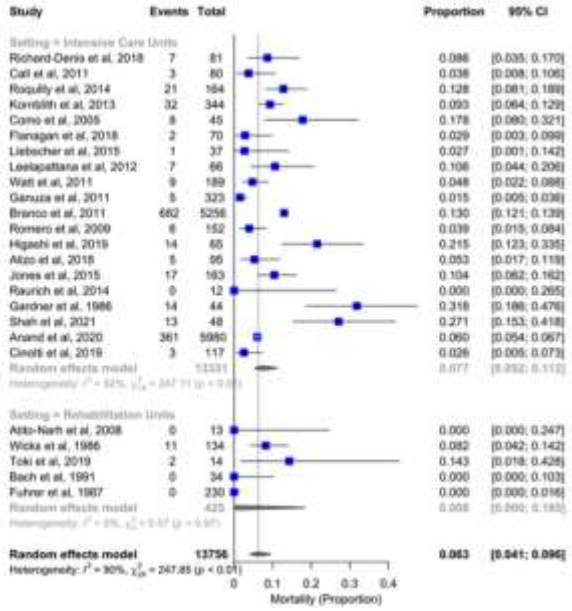


Figure 3. Forest plot for mortality. Studies are presented according to setting classification (intensive care units vs. rehabilitation units): both overall and subgroup estimates are reported.



<table>
<tr><td></td><td colspan="2">Figures are extracted from the original article (Schreiber et al. 2021), which is licensed under Creative Commons Attribution 4.0 International License.</td></tr>
<tr><td rowspan="2">Wang et al. 2020
China

Review published articles up to May 2019

N = 16

Level of evidence:
The Cochrane Collaboration risk of bias tool

Type of study:
RCTS

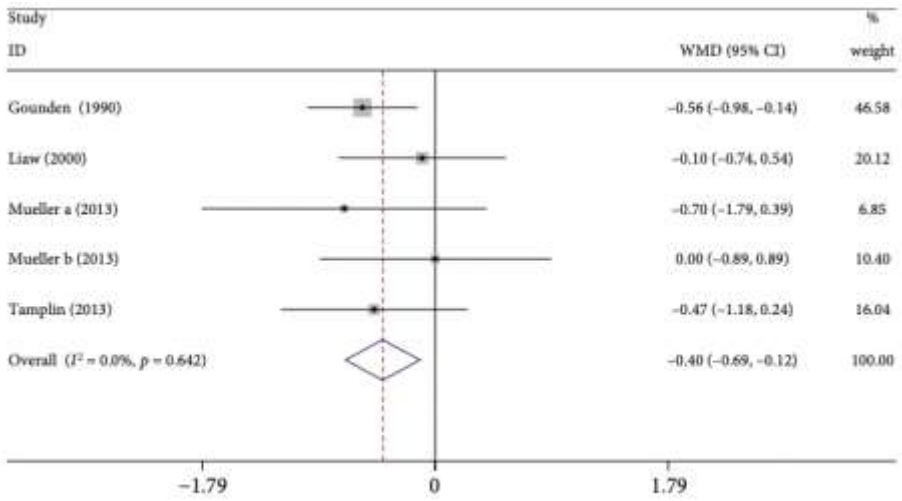
AMSTAR: 7</td><td>Methods: To investigate the pulmonary function responses to respiratory muscle training (RMT) in people with tetraplegia.
Databases: PubMed, Embase, Cochrane Library, CNKI, Wanfang Data, and VIP.</td><td>1. 237 patients and 211 controls were included in the review. Nine studies used inspiratory muscle training (IMT) or expiratory muscle training (EMT); and seven used IMT and EMT.
2. Meta-analysis showed that compared to the control, RMT did not improve FEV_1 (WMD: -0.26, 95% CI -0.54 to -0.02, P = 0:07, I^2 = 63.8%)), but RMT significantly improved:
a. VC (WMD: -0.40, 95% CI -0.69 to -0.12, P = 0.006, I^2 = 0%).
b. FVC (WMD: -0.43, 95% CI -0.84 to -0.03, P = 0.037, I^2 = 80%).
c. MEP (WMD: -13.08, 95% CI -23.78 to -2.37, P = 0:017, I^2 = 65.7%).
d. MVV (WMD: -5.89, 95% CI -10.63 to -1.14, P = 0:015, I^2 = 43.1%).
e. MIP (WMD: -13.14, 95% CI -18.01 to -8.27, P < 0:001, I^2 = 19.9%).</td></tr>
<tr><td colspan="2">Forest plot of meta-analysis results for VC.
 

FIGURE 3: Forest plot of meta-analysis results for vital capacity.

Forest plot of meta-analysis results for FVC.</td></tr>
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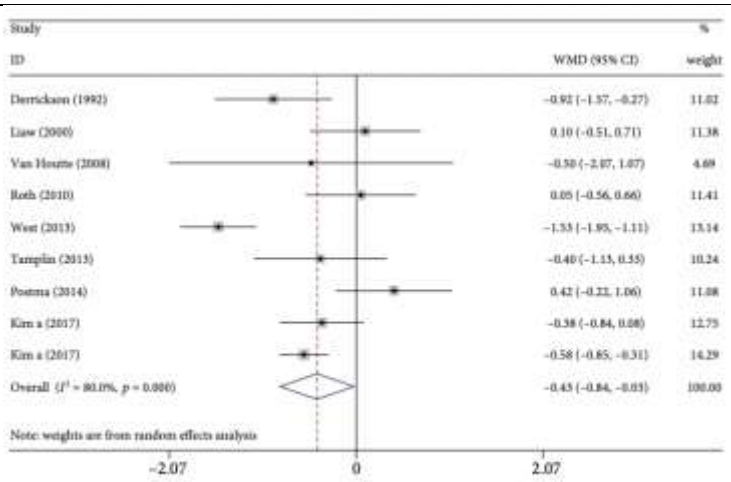

FIGURE 4: Forest plot of meta-analysis results for force vital capacity.

Forest plot of meta-analysis results for FVC1.

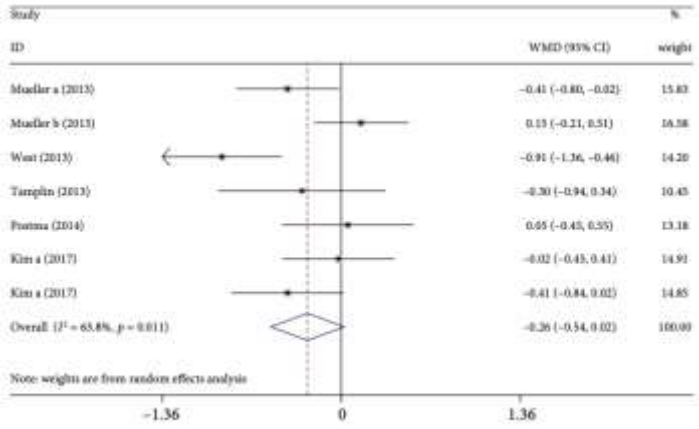

FIGURE 5: Forest plot of meta-analysis results for forced expiratory volume in 1 second.

Forest plot of meta-analysis results for maximum static expiratory pressure.

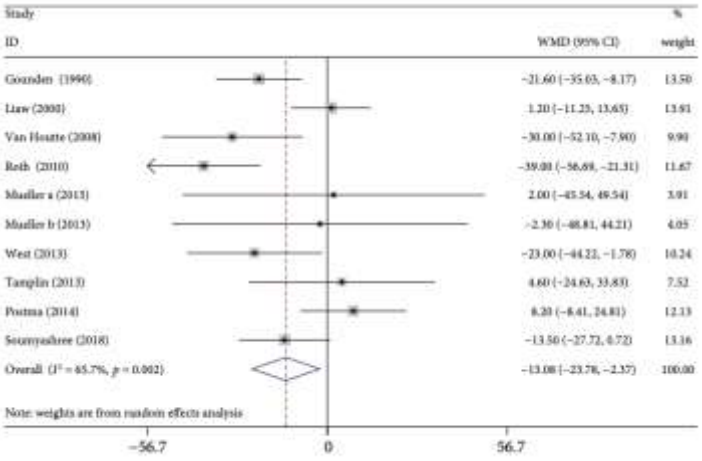

FIGURE 6: Forest plot of meta-analysis results for maximum static expiratory pressure.

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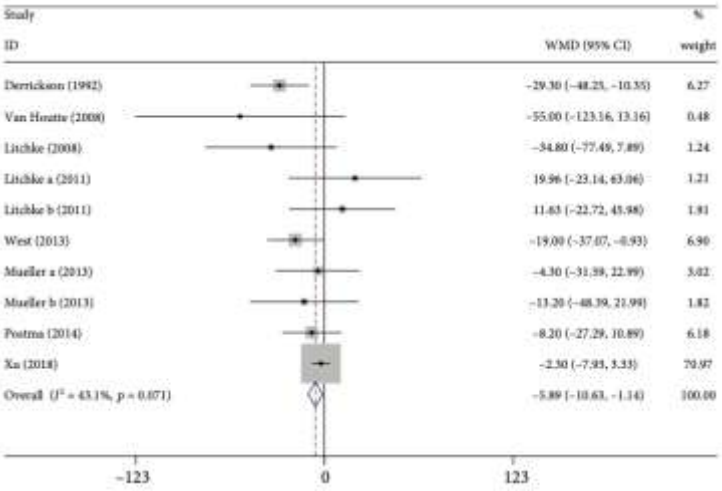
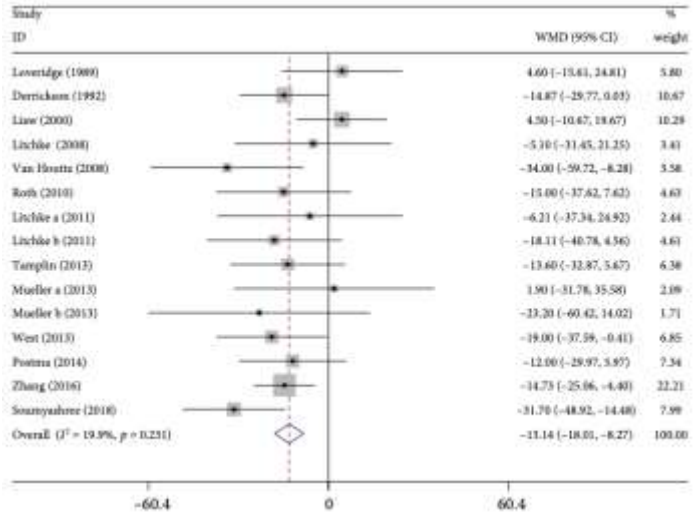
Forest plot of meta-analysis results for MVV.


Forest plot of meta-analysis results for maximum static inspiratory pressure.


Figures are extracted from the original article (Wang et al. 2020), which is licensed under Creative Commons Attribution License.
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<tr>
<td>Lemos et al. 2020
Brazil
Reviewed published articles up to August 2018.
N = 17
Level of evidence:
PEDro scale
Type of study:
Experimental (controlled, non-</td>
<td>Method: Reviewed new and emerging research related to the effects of RMT on pulmonary function, respiratory muscle strength and endurance, and cardiorespiratory fitness of athletes and non-athletes with SCI, and present an updated frequency, intensity, time, and type principle to RMT.</td>
<td>1. Training methods varied; 6 studies adopted the IMT; 6 used the RMT with bidirectional resistance; 3 had the EMT; 2 studies applied normocapnic hyperpnoea training.
2. RMT improves pulmonary function and respiratory muscle strength and endurance in athletes and non-athletes with SCI, although no associations were found between the RMT and cardiorespiratory fitness (i.e., VO_2max).</td>
</tr>
</table>

controlled and cross-over) studies AMSTAR: 5	**Database:** PubMed, Lilacs, Scopus, Web of Science, PEDro, SciELO and Cochrane.	3. Even though 7/17 studies scored ≥ 6 in the PEDro scale, more research is needed with greater sample sizes, standardization of methods and interventions.
McCaughey et al. 2016 Australia Reviewed published articles until 23 December 2014 N = 14 **Level of evidence:** N/A **Type of study:** Self-control (randomized crossover) and RCTs AMSTAR: 7	**Methods:** Systematic review and meta-analysis made to identify whether abdominal functional electrical stimulation (FES) is an effective intervention to improve respiratory function in both an acute and chronic manner after SCI. **Databases:** Pubmed. **Protocols of abdominal FES used:** The median maximum amplitude was 100 mA (range 100–450 mA), the mean pulsewidth (pulse duration) was 259 μs (range 25–400 μs) and almost all studies used a stimulation frequency of 50 Hz. There was a lack of homogeneity in electrode position, with a range of positions used to stimulate either or both the rectus abdominis and external oblique muscles.	1. Low participant numbers and heterogeneity across studies reduced the power of the meta-analysis (141 participants were included in total (n = 128 receiving abdominal FES; n = 13 acting as controls). 2. 10 studies assessed acute respiratory effects of abdominal FES and showed a significant acute improvement in cough peak flow (CPF) whereas FEV_1 approached significance. 3. 4 studies assessed chronic respiratory effects of FES; showing only a significant increase and effect in FVC (P = 0.043), with a continued improvement after training; in VC (P = 0.013); and in PEF (P = 0.026).
Berlowitz & Tamplin 2013 (Tamplin & Berlowitz 2014) Australia Reviewed published articles (searches were not restricted by date, language, or publication status) N = 11 **Level of evidence:** PEDro scale was used to evaluate studies **Type of study:**	**Method:** Systematically review the effectiveness of RMT on pulmonary function, dyspnea, respiratory complications, respiratory muscle strength, and quality of life (QOL) for people with cervical SCI. There were no date, language, or publication restrictions. Only RCTs were included. **Database:** Cochrane Injuries and Cochrane Neuromuscular Disease Groups' Specialized Register, the Cochrane Central Register of	1. 11 RCTs with 212 participants with cervical SCI were included. 2. Meta-analysis revealed a statistically significant effect of RMT for 3 outcomes: VC (MD mean end point 0.4L, 95% CI 0.1 to 0.7), MIP (MD mean end point 10.5 cmH_2O, 95% CI 3.4 to 17.6), and MEP (MD mean end point 10.3 cmH_2O, 95% CI 2.8 to 17.8). (Berlowitz & Tamplin 2013). 3. Meta-analysis revealed a statistically significant effect of RMT for 2 extended outcomes: MVV (MD mean end point 17.51L/min, 95% CI 5.20 to 29.81), and IC (MD mean end point 0.35L, 95% CI 0.05 to 0.65) (Tamplin & Berlowitz, 2014). 4. RMT showed a combined benefit in VC and FVC (MD mean end point 0.41L, 95%

RCTs AMSTAR: 10	Controlled Trials (CENTRAL) (2012, Issue 1), MEDLINE, EMBASE, CINAHL, ISI Web of Science, PubMed, and clinical trials registries (Australian New Zealand Clinical Trials Registry, Clinical Trials, Controlled Trials metaRegister), and hand searching.	CI 0.17 to 0.64) (Tamplin & Berlowitz, 2014). 5. There was no effect on FVC_1 or dyspnoea. 6. The results from QOL assessment tools could not be combined from the three studies for meta-analysis. 7. No adverse effects as a result of RMT were identified in cervical SCI.
Wadsworth et al. 2009 Australia Reviewed published articles from databases' inception to March 2008 N = 11 **Level of Evidence:** PEDro scale **Type of study:** 5 crossover randomized 1 crossover pseudorandomized 1 crossover 4 within-patient AMSTAR: 9	**Methods:** Literature search for randomized control and randomized crossover studies reporting the effects of AB in people with acute or chronic SCI. Interventions included different types of AB. **Databases:** MEDLINE, CINAHL, Cochrane, EMBASE, PEDro.	1. Some evidence that the use of an abdominal binder improves VC (by WMD 0.32 L, 95% CI 0.09 to 0.55) but decreases FRC (by WMD 0.41 L, 95% CI 0.14 to 0.67) when assuming the sitting or tilted position. 2. AB did not influence total lung capacity (TLC). 3. PEDro mean score of 4.3/8. 4. Available evidence is not yet sufficient to either support or discourage the use of an AB in this patient population.
Reid et al. 2010 Canada Reviewed published articles from databases' inception to May 2009 N = 24 **Level of Evidence:** PEDro scale – RCTs **Type of study:** 2 RCT 3 prospective controlled 9 pre-post 3 retrospective case series 7 case reports	**Methods:** Literature search for English articles assessing physical therapy secretion removal techniques **Databases:** MEDLINE/PubMed, CINAHL, EMBASE, and PsycINFO.	1. Level 4/5 evidence supports the use of secretion removal techniques in people with SCI. 2. Level 2 evidence (from 1 prospective controlled trial) and level 4 evidence (based on 2 pre-post studies) support the effectiveness of abdominal binders for assisted breathing. 3. Level 1 evidence that RMT improves respiratory muscle strength and decreases the number of RI, both of which infer improved airway clearance. 4. Level 4 evidence based on 2 pre-post trials and level 5 evidence from 2 case reports support the use of electrical stimulation (ES) of the lower thoracic-lumbar spinal cord (T9, T11, and L1) and the abdominal wall muscles to improve expiratory flow rates during cough.

AMSTAR: 6		5. Level 2 (based on 2 prospective controlled trials) and level 4 (based on 1 pre-post trial) evidence support the effectiveness of assisted coughing by manual abdominal compression. 6. Insufflation combined with manual assisted cough provides the most consistent evidence for improving cough and/or PEFR.
Sheel et al. 2008 Canada Review published articles from 1980 to 2006 N = 13 **Level of Evidence:** PEDro scale – RCTs **Type of study:** 3 RCTs 1 pre-post 6 case series 2 cohort 1 case report AMSTAR: 6	**Methods:** Literature search for articles assessing exercise training and IMT for the improved respiratory function of patients with SCI. **Databases:** MEDLINE/ PubMed, CINAHL, EMBASE, PsycINFO.	1. There is Level 2 evidence supporting exercise training as an intervention to improve respiratory strength and endurance. 2. There is Level 4 evidence to support exercise training as an intervention to improve resting and exercising respiratory function in people with SCI. 3. There is Level 4 evidence to support IMT as an intervention to decrease dyspnea and improve cardiovascular function in people with SCI.
Van Houtte et al. 2006 Belgium Reviewed published articles from 1980 to November 2004 N = 21 **Level of Evidence:** Modification of the framework for methodological quality developed by Smith et al. and Lotters et al. - Max score of 40 **Type of study:** 6 controlled studies 15 non controlled studies AMSTAR: 5	**Methods:** Literature search for articles assessing the effectiveness of RMT on people with SCI. **Databases:** MEDLINE (National Library of Medicine, Bethesda, MD, USA) database (from 1980 to November 2004) and relevant references from peer-reviewed articles.	1. RMT tended to improve expiratory muscle strength, VC, and residual volume (RV). 2. Insufficient data was available to make conclusions concerning the effects on inspiratory muscle strength, respiratory muscle endurance, QOL, exercise performance and respiratory complications.
Giannoccaro et al. 2013 Italy	**Method:** Reviewed the prevalence, features, and treatment of sleep disorders in SCI. Only	1. Little has been published on the treatment of obstructive sleep apnea (OSA) in patients with SCI, but some patients with SCI have been reported to

Reviewed published articles up to October 2012. N = 113 **Level of evidence:** Methodological quality was not assessed **Type of study:** Types of studies included not specified. AMSTAR: 1	studies published in English were included. **Database:** PubMed.	respond to weight reduction, whereas changing sleep position is a more difficult measure to apply to these patients. 2. Two studies reported poor compliance with CPAP in patients with SCI with a significantly lower acceptance rate of 23-30% in higher level complete tetraplegic patients than the 60-80% acceptance described in non-SCI patients. However, data on long-term CPAP in one survey showed that 63% of patients used the treatment regularly. 3. A study reported that despite no significant difference in AHI between people with tetraplegia and non-SCI controls, the non-SCI people required significantly higher levels of CPAP to control their OSA than patients with tetraplegia, more than two thirds of whom (68.8%) required less than 10 cmH_2O of CPAP. This suggests that additional unknown factors may contribute to the high prevalence of OSA in tetraplegia.

6 Pharmaceutical Interventions

6.1 Airway Hyperresponsiveness and Bronchodilators

People with SCI may have a restrictive ventilatory impairment that is primarily dependent upon the level and completeness of injury. However, there is also a body of evidence that patients with cervical SCI have a component of obstructive ventilatory impairment.

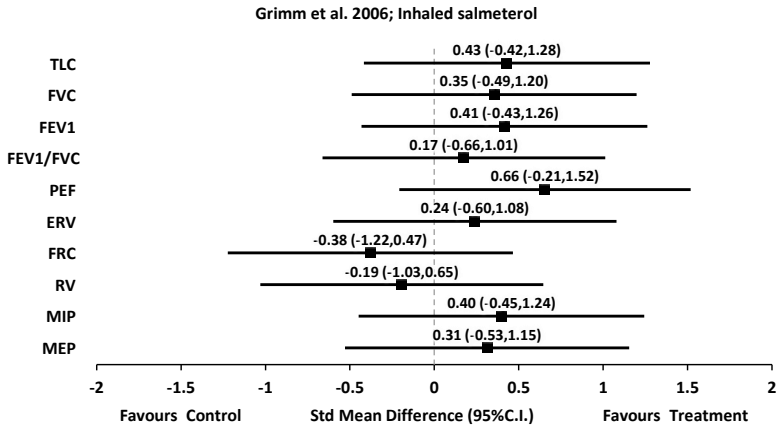
People with tetraplegia demonstrate bronchial hyperresponsiveness to multiple agents including methacholine, histamine and distilled water (Dicpinigaitis 1994a; Singas et al. 1996; Fein et al. 1998; Grimm et al. 1999; Singas et al. 1999). There are several potential mechanisms for hyperresponsiveness in tetraplegia including loss of sympathetic autonomic input with relatively unopposed parasympathetic input (Dicpinigaitis et al. 1994a; Grimm et al. 1997; Singas et al. 1999), altered mechanical lung properties with decreased deep breathing and "stretching" of airways (Singas et al. 1999), and nonspecific airway hyperresponsiveness similar to people with asthma (Grimm et al. 1997).

Despite evidence regarding the presence of airway hyperresponsiveness in tetraplegia, the use of anticholinergic bronchodilators such as ipratropium and beta 2 selective agonists such as metaproterenol in SCI has not been well studied. The use of bronchodilators is routinely recommended as add-on therapy in other conditions with airway hyperreactivity such as chronic obstructive pulmonary disease (COPD) and asthma, but it is not clear if these recommendations can be generalized to the SCI population.

For people on MV, bronchodilators are routinely administered to relieve dyspnea and reverse bronchoconstriction. They can be administered by metered-dose inhaler or by nebulizer. Again, the long-term use of bronchodilators and the best route of administration in mechanically ventilated people with SCI have not been studied.

The measurement of airway responsiveness with inhaled bronchoconstrictor stimuli such as methacholine or histamine involves the patient inhaling increasing doses or concentrations of a stimulus until a given level of bronchoconstriction is achieved, typically a 20% fall in FEV_1. Airway responsiveness is then expressed as the dose or concentration of the stimulus required to achieve this degree of bronchoconstriction (PD_{20} and PC_{20}, respectively).

Table 3. Bronchodilators

Author Year Country Research Design Score Sample Size	Methods	Outcome
Grimm et al. 2006 USA RCT (crossover) PEDro = 6 Level 1b N initial = 13 N final = 11	**Population:** 13 males; mean (SD) age: 40 (8) yrs; DOI 18(10) yrs; complete and incomplete, C4-C7. **Treatment:** Salmeterol inhalation (50 µg) **Outcome Measures:** Spirometric and lung volume parameters, MIP, and MEP.	1. Regardless of administration order with placebo, salmeterol was associated with a significant increase in FVC, FEV_1, PEFR, MIP and MEP compared with placebo and baseline. 2. ERV increased significantly during salmeterol administration compared to baseline.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data. 	
Schilero et al. 2004 USA Pre-post Level 4 N = 10	**Population:** 5 tetraplegia (C4-C7), 2 complete, 3 incomplete, mean(SD) age:45(16) yrs, 17(8) yrs post-injury; 5 paraplegia (below T5), 2 complete, 3 incomplete, age:40(9) yrs, 19(10) yrs post-injury.	1. In people with tetraplegia, inhaled metaproterenol resulted in significant increase in specific airway conductance and significant increases in FEV_1 and forced expiratory flow 25-75%.

	Treatment: Inhalation of 0.3 mL of 5% solution of metaproterenol sulfate via nebulizer. **Outcome Measures:** Spirometry and specific airway conductance as measured by body plethysmography pre- and post-bronchodilator.	2. In people with paraplegia, inhaled metaproterenol resulted in significant increase in specific airway conductance although the increase was considerably less than that seen in tetraplegia. There was no significant change in FVC, FEV_1 and forced expiratory flow 25-75%.
Grimm et al. 1999 USA Pre-post Level 4 N = 15	**Population:** 9 tetraplegia (C4-C7) and 6 paraplegia (T9-L1), 4 complete & 11 incomplete, all male, age:25-61yrs, 4-32yrs post-injury **Treatment:** Increasing duration of exposure time to ultrasonically nebulized distilled water (UNDW). 5 participants responding to UNDW returned on a separate day for UNDW challenge following the inhalation of aerosolized ipratropium bromide. **Outcome Measures:** Spirometry, PD_{20}	1. 8/9 tetraplegic participants (known histamine response positive) had a significant bronchoconstrictor response to UNDW (PD_{20} 7.76 +/- 7.67 mL). 2. 0/6 paraplegic participants (known histamine response negative) demonstrated a response to UNDW (PD_{20} 24 mL). 3. 5/5 tetraplegic responders to UNDW no longer responded after pretreatment with ipratropium bromide.
Singas et al. 1999 USA Prospective controlled trial Level 2 N = 25	**Population:** 25 tetraplegia (C4-C7): 10 complete & 15 incomplete, all males, age range:23-63yrs, 1-40yrs post-injury, 12 maintained on oral oxybutynin & 13 age-matched controls. **Treatment:** 6/12 oxybutynin participants were challenged with methacholine, & 6/12 with histamine; 7/13 control participants were challenged with methacholine & 6/13 with histamine. Increasing concentrations of aerosolized histamine or methacholine were administered. **Outcome Measures:** Spirometry, PC_{20}.	1. All 13 control participants (methacholine and histamine) and all 6 oxybutynin-histamine participants had a significant bronchoconstrictor response (PC_{20}<8 mg/mL). 2. The oxybutynin-methacholine participants had a normal response to methacholine. (PC_{20}>=25 mg/mL).
Fein et al. 1998 USA Pre-post Level 4 N = 15	**Population:** 15 tetraplegia (C4-C7): 5 complete and 10 incomplete, all male, age range: 24-64yrs, DOI range: 3-31 yrs **Treatment:** Increasing inhaled concentrations of aerosolized histamine diphosphate. Responders to histamine were retested on a separate day after pre-treatment with ipratropium bromide 72 mcg.	1. 12/15 participants had a significant bronchoconstrictor response to aerosolized histamine (geometric mean PC_{20} 1.27 mg/mL). 2. There were no significant differences in FVC and FEV_1 values between responders and non-responders. 3. All 12 participants initially responsive to histamine were again hyperresponsive at the time of rechallenge following

	Outcome Measures: Spirometry, PC_{20}.	ipratropium (geometric mean PC_{20} 1.50 mg/mL).
Grimm et al. 1997 USA Prospective controlled trial Level 2 N = 24	**Population:** tetraplegia (C4-C7), all male, age range: 23-65, time since injury range: 2-29 yrs, 14 on chronic oral baclofen and 10 age-matched controls **Treatment:** Administration of histamine by inhaler in 14 baclofen participants and 10 controls. Administration of methacholine in 4 baclofen participants and 5 controls. **Outcome Measures:** Spirometry, PC_{20}.	1. 11/14 participants on baclofen and 8/10 control participants had significant bronchoconstrictor response to histamine. 2. There was no significant difference in mean PC_{20} between the baclofen and control groups (mean(SD) PC_{20}= 2.91(2.3) and PC_{20} =2.18(1.9), respectively). 3. The methacholine and histamine PC_{20} were almost identical in controls. ¾ baclofen participants had significantly different responses to methacholine and histamine.
Almenoff et al. 1995 USA Pre-post Level 4 N=25	**Population:** 25 tetraplegia: 6 complete,19 incomplete, all male, mean (SD) age: 43(3) yrs, 11(2) yrs post-injury. **Treatment:** Administration of 72 mcg ipratropium bromide by inhaler with spacer. **Outcome Measures:** Spirometry pre- and post-bronchodilator (improvement in FVC or FEV_1>=12%).	1. 48% of participants had a positive bronchodilator response (6/10 smokers and 6/15 non-smokers). 2. There were no significant correlations between the response to ipratropium and dyspnea at rest, smoking history, or sensory completeness of cord lesion.
Dicpinigaitis et al. 1994b USA Prospective controlled trial Level 2 N = 14	**Population:** tetraplegia (C4-C7); all male, age range 23-57 years, 6 on chronic oral baclofen and 8 controls **Treatment:** Administration of increasing concentrations of nebulized methacholine. **Outcome Measures:** Spirometry, PC_{20}.	1. 8 out of 8 control participants showed significant bronchoconstrictor response to methacholine (mean(SD) PC_{20}= 1.42(1.6)). 2. 2 out of 6 baclofen participants had borderline to mild bronchoconstrictor response to methacholine. 4/6 baclofen participants did not respond to methacholine (mean(SD) PC_{20}= 15.0(9.1) for baclofen group). There was no correlation between PC_{20} and dosage or duration of baclofen.
Spungen et al. 1993 USA Pre-post Level 4 N = 34	**Population:** tetraplegia: 34 males, all motor complete, non-smokers' mean(SD) age:40(5) yrs, smokers' age: 48(3) yrs, 11.8(1.6) yrs since injury. **Treatment:** Inhalation of 2.5 ml metaproterenol sulfate inhalation solution. **Outcome Measures:** Spirometry pre- and post-bronchodilator (improvement in FEV_1>=12%).	1. 41% of participants demonstrated a significant response in FEV_1 to inhaled metaproterenol (5/12 non-smokers and 9/22 smokers). 2. In the non-smokers, the correlation of FVC and FEV_1 with level of lesion was positive and significant prior to administration of bronchodilator and became more significant post-bronchodilator. 3. In the smokers, FVC and FEV_1 failed to significantly correlate with level of lesion.

Discussion

Ipratropium, metaproterenol, salbutamol and salmeterol have been studied in SCI. All drugs have shown a positive effect with improvements in FEV_1 in people with tetraplegia.

Almenoff et al. (1995) showed that 48% of people with tetraplegia given inhaled ipratropium bromide responded with greater or equal to 12% improvement in FEV_1 and/or FVC. Spungen et al. (1993) found that 41% of people with tetraplegia responded to metaproterenol with a greater or equal to 12% improvement in FEV_1, similar to Schilero et al. (2004), who also found a significant improvement in FEV_1 in people with tetraplegia treated with metaproterenol. An RCT performed by Grimm et al. (2006) showed four week administration of salmeterol, a longer acting beta 2 agonist, to be associated with improved pulmonary parameters (FVC, FEV_1, PEFR, MIP and MEP) in people with tetraplegia. Beta 2 agonists have been shown to have anabolic effects in other muscles in SCI (Signorile et al. 1995). The increases in MIP and MEP seen with salmeterol suggest the possibility of a similar anabolic effect on the respiratory muscles.

Salbutamol, ipratropium, and metaproterenol appeared to be effective in improving short-term pulmonary function, and salmeterol in the longer-term. There are concerns that ipratropium's anticholinergic effects could cause thickening of secretions and block release of surfactant which could compromise its ultimate effects on respiratory function (Consortium for Spinal Cord Medicine 2005).

With the exception of the single level 1 study in support of salmeterol in chronic SCI, the literature consists of level 4 evidence supporting the use of bronchodilators in SCI. However, the recommendations for the use of bronchodilators in asthma and COPD are well supported by the literature and there is a strong likelihood that SCI shares some clinical and pathophysiologic similarities to those conditions. Nevertheless, it is important to recognize that literature in SCI remains lacking.

In addition to traditional bronchodilators, there is evidence that airway hyperresponsiveness in tetraplegia can be modulated by medications used for other conditions in SCI, such as baclofen and oxybutynin. Baclofen, a GABA agonist, is commonly used to treat spasticity. GABA receptors have been found in peripheral tissue, including lung, raising the possibility that baclofen may have the potential to affect airway hyperreactivity. Oxybutynin, a medication used to treat bladder spasms, has the potential to affect airway hyperreactivity through its anticholinergic properties. The effects of both baclofen and oxybutynin have been studied in small, controlled trials in tetraplegia. In each study, the study group was a group of people who were already maintained on the medications for the usual indications. The studies did not look at the bronchodilator effects of the medications but focused on their ability to block bronchoconstrictor challenges to methacholine and histamine.

Pre-treating tetraplegic patients with inhaled ipratropium bromide blocked hyperresponsiveness to methacholine (Dicpinigaitis 1994a). Baclofen and oxybutynin also decreased hyperresponsiveness to methacholine (Dicpinigaitis et al. 1994b; Grimm et al. 1997; Singas et al. 1999). In contrast, pre-treating patients with tetraplegia with inhaled ipratropium bromide did not block hyperresponsiveness to histamine (Fein et al. 1998). Similarly, oxybutynin and chronic oral baclofen did not block hyperresponsiveness to histamine in tetraplegia (Grimm et al. 1997;

Singas et al. 1999). Although these results are intriguing, the results of these small studies cannot necessarily be extrapolated to the clinical situation where a bronchodilator effect is required.

There are no long-term studies on the use of bronchodilators in SCI. Further studies on the selection of bronchodilators, route of administration and role in long-term MV in SCI should be undertaken. Studies looking at the clinical effects of other commonly used SCI medications with potential bronchodilator effects such as baclofen and oxybutynin are warranted.

Conclusion

There is level 4 evidence (from three pre-post studies: Almenoff et al. 1995; Spungen et al. 1993; Schilero et al. 2004) that ipratropium and metaproterenol have a positive effect on pulmonary function in people with tetraplegia.

There is level 1 evidence (from one RCT: Grimm et al. 2006) that salmeterol has a positive effect on pulmonary function in people with tetraplegia.

There is level 2 evidence that chronic oral baclofen and chronic oxybutynin (from two prospective controlled trials and one pre-post study: Dicpinigaitis 1994b; Grimm et al. 1997; Singas et al. 1999) and level 4 evidence that ipratropium bromide (Dicpinigaitis 1994a) decrease or block hyperresponsiveness to methacholine, but not histamine in tetraplegia.

Key Points

The use of bronchodilators should be considered in people with tetraplegia who demonstrate an element of obstructive airway impairment.

The effects of other medications commonly used in the management of SCI such as baclofen and oxybutynin should be considered when reviewing airway hyperreactivity in people with tetraplegia.

6.2 Anabolic Agents

Anabolic steroids are derivatives of testosterone. Their exact physiologic effects on the respiratory system are unclear, but they have been studied as a possible treatment in COPD, especially for their role in potentially increasing muscle mass.

Anabolic steroids have potentially serious side effects, including effects on liver function, lipid profile, and the reproductive system. The long-term safety of anabolic steroids such as oxandrolone in SCI has not been established.

Table 4. Anabolic Steroids

Author Year Country Research Design Score Sample Size	Methods	Outcome
Halstead et al. 2010 USA Pre-post Level 4 N = 10	**Population:** 10 males; tetraplegia; SCI injury C5-C8; 7 AIS A, 3 AIS B, age 32.5; DOI 8.8. **Treatment:** Oxandrolone (20 mg/day orally in divided doses, 8 weeks). **Outcome Measures:** FVC, FEV_1, FEV_1/FVC, PEFR, maximum ventilator volume (MVV).	1. Following treatment there were non-significant increases in FVC by 3.3%, FEV_1 by 3.1% and MVV by 9.3%; and a non-significant decrease in PEFR by 3.4%. 2. Administration of oxandrolone over 8 weeks had no effect on pulmonary function.
Spungen et al. 1999 USA Pre-post Level 4 N = 10	**Population:** 10 tetraplegia (C4-5), motor complete, all male, mean(SD) age: 41(9) yrs, 16(8) yrs post-injury. **Treatment:** Administration of oxandrolone 20 mg/day for 1 month. **Outcome Measures:** Weight gain, spirometry, MIP, MEP, resting self-rate of dyspnea (Borg scale), serum lipid profiles and liver function tests.	1. On average, participants gained 1.4(1.5) kg (2(2)%). 2. A significant improvement was seen in combined measures of spirometry (9(2)%). 3. A significant improvement was seen in MIP (10(7)%). The improvement in MEP was not significant (9(13)%). 4. Borg scale decreased by an average of 37(28)%.

Discussion

There are two studies in the literature on the effects of anabolic steroids on pulmonary function in SCI. Spungen et al. (1999) treated 10 men with motor complete C4-C5 tetraplegia with a one month course of oxandrolone, an oral anabolic steroid. Following oxandrolone, significant improvements were seen in weight gain, FVC, FEV_1 and forced inspiratory vital capacity. There was a significant increase in MIP from baseline and a non-significant increase in maximal expiratory pressure (PE_{max}). Participants experienced a significant decrease in subjective dyspnea. There was no long-term follow-up to see if any of the improvements were permanent. Halstead et al. (2010) treated 10 male participants with motor complete tetraplegia with oxandrolone for 8 weeks and found non-significant improvements in lung function.

Conclusion

There is conflicting evidence (Spungen et al. 1999; Halstead et al. 2010) that the short-term use of oxandrolone improves pulmonary function in people with tetraplegia.

Key Points

The short-term use of oxandrolone can be considered to improve pulmonary function in people with tetraplegia.

6.3 Other Pharmaceuticals

There are many other medications with potential benefit for the treatment of pulmonary function in SCI. The use of anticoagulants for the prevention of deep vein thrombosis and pulmonary emboli is covered here. Other medications used in the treatment of asthma and/or COPD such as cromolyn sodium, methylxanthines and inhaled corticosteroids have not been studied in SCI.

Table 5. Other Pharmaceuticals

Author Year Country Research Design Score Sample Size	Methods	Outcome
Vivodtzev et al. 2021 USA Case control Level 3 N = 21	**Population:** 21 patients with (< 2 years) high-level (C4 - T3) SCI who were enrolled in an exercise program employing FES - row training (FESRT) (as part of rehabilitation), were retrospectively divided into 2 groups: buspirone group (n = 10) and control group (n = 10). *Buspirone group:* mean (SD) age 32 (± 10), mean (SD) time since injury 1.0 (± 0.4) years, AIS A (n = 5), AIS B (n = 3), and AIS C (n = 2). *Control group:* mean (SD) age 28 (± 5), mean (SD) time since injury 1.2 (± 0.4) years, AIS A (n = 6), AIS B (n = 2), and AIS C (n = 3). **Treatment:** FESRT for 6 months with a naturalistic group division between those taking Buspirone or not. ● Buspirone group: Patients took an average of 29 ± 17 mg/day of Buspirone. ● Control group: None of the participants had buspirone. **Outcome Measures:** Cardiopulmonary exercise testing during FES-Rowing and a pulmonary function test before and after their 6-month FESRT program. VO_2, VCO_2, respiratory exchange ratio (RER), expired O_2 and CO_2 gas fractions, V_E, V_T, HR, peak lactate assessment, FEV_1, FVC each within 200 mL, and ERV.	1. After training, Buspirone group tended to have a significantly greater increase in VO_2peak than the control group (+ 0.24 ± 0.23 vs. + 0.10 ± 0.13 L/ min, p = 0.08), although in both groups ($p \leq$ 0.04) this parameter increased. 2. There was also a significantly greater increase in $V_E$peak after training in Buspirone compared to Control (+ 6.5 ± 8.1 vs. − 0.7 ± 6.9 L/min, $p <$ 0.05). 3. Those on Buspirone improved V_T after training compared to baseline ($p <$ 0.01), while it was not changed in the control group (p = 0.63). As a result, those on Buspirone tended to breathe deeper compared to Control (p = 0.06). 4. Furthermore, changes in FVC and FEV_1 were significantly correlated with those in $V_T$peak in Buspirone ($r > 0.66$, $p < 0.05$).

Discussion

One retrospective study had patients with high-level SCI perform an FES and rowing training intervention; those who took Buspirone, a medication used to help relieve anxiety, breathed deeper and had more improvements in cardiorespiratory (VO_2peak) and respiratory parameters

($V_E$peak and V_T) compared to patients who performed the same FES and rowing training but did not take Buspirone (Vivodtzev et al. 2021). Double-blind, randomized controlled trials with at least 20 participants per group would be helpful to experimentally determine if Buspirone has a generalizable effect on respiration in people with SCI.

Conclusion

There is level 3 evidence (from one case control study: Vivodtzev et al. 2021) that Buspirone during a period of 6 months of FESRT provided more improvements in some cardiorespiratory and respiratory parameters than FESRT alone in patients with acute high-level SCI.

7 Mechanical Ventilation (MV) and Weaning Protocols

The indications for MV and the acute management of respiratory issues in SCI are outside the scope of this review which focuses on rehabilitation (Acute Respiratory and Mechanical Ventilation and Weaning Protocols may be found here). However, the long-term complications associated with chronic ventilator dependency need to be mentioned to highlight their importance. The overall life expectancy for people with SCI who are ventilator dependent has been increasing, especially for those who survive the first year following injury (DeVivo & Ivie 1995). Despite advances, mortality for people with ventilator dependency remains high (Shavelle et al. 2006; DeVivo & Ivie 1995).

In general, people with complete neurologic injuries at C2 and above have no diaphragmatic function and are often ventilator dependent. People with complete neurologic injuries at C3 or C4 have variable diaphragmatic function. Although they may have the potential for ventilator weaning, it is difficult to predict whether they will ultimately be successfully weaned. Research suggests that trends in improved survival observed in SCI were not seen among ventilator-dependent patients with SCI surviving the first few years post-injury, and that ventilator dependency is an independent risk factor for mortality (Shavelle et al. 2006). People with complete injuries at C5 and below typically have intact diaphragmatic function. They may require ventilatory support initially post-injury but are usually able to wean from the ventilator.

The approach to ventilator weaning in SCI remains an important and somewhat neglected issue. There is a distinct lack of controlled trials in respiratory medicine; research in this area primarily consists of retrospective reviews and small case series. The Paralyzed Veterans of America (PVA) Consortium for Spinal Cord Medicine—Respiratory management following spinal cord injury: a clinical practice guideline for health-care professionals (2005) suggests the consideration of "…progressive ventilator free breathing (PVFB) over synchronized intermittent mandatory ventilation (IMV)". The other clinical practice guideline that we are aware of addressing SCI is the Home mechanical ventilation: A Canadian Thoracic Society clinical practice guideline. This guideline intends to provide up-to-date information and evidence-based recommendations re: preventive airway management and home ventilation with regards to a variety of conditions with respiratory consequences.

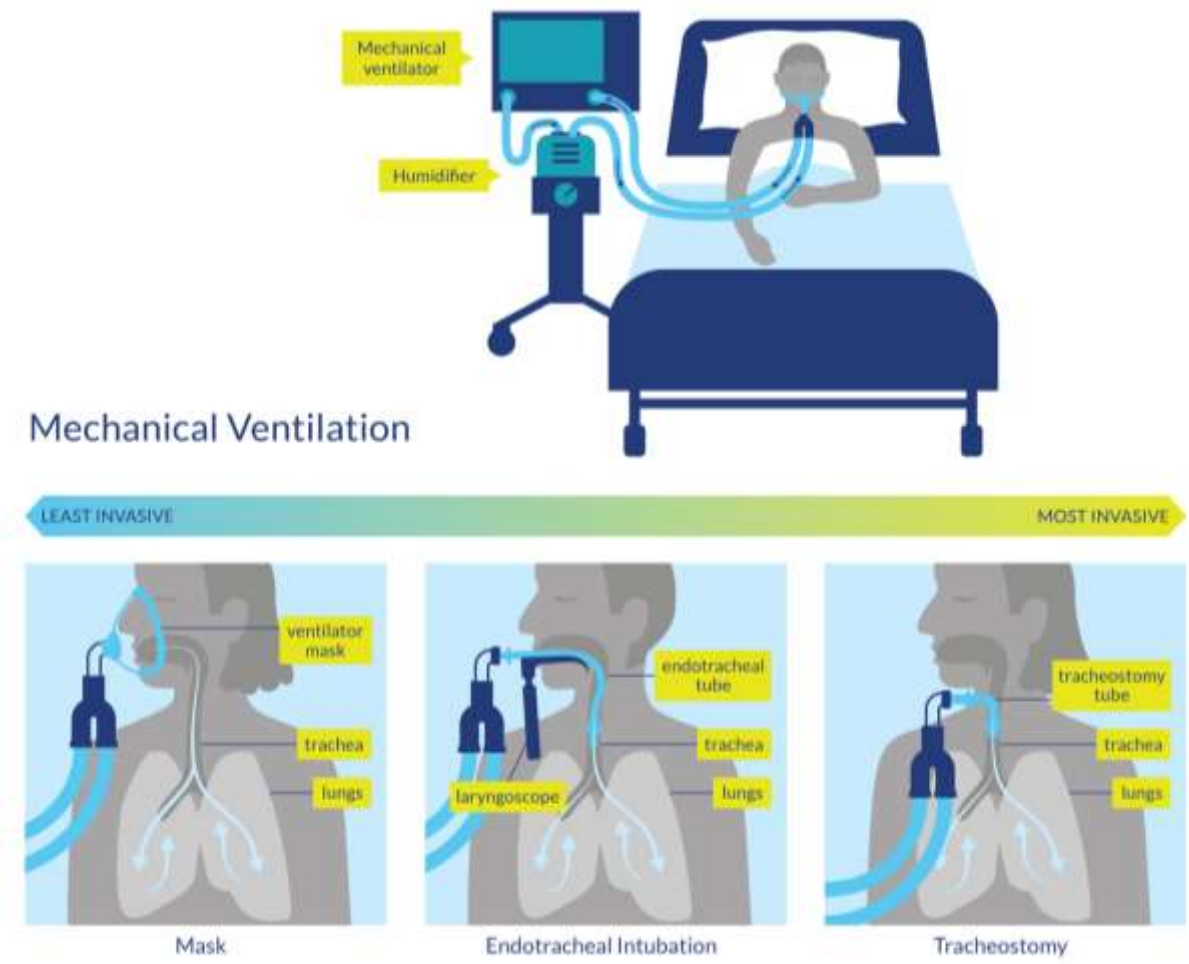


Figure 3. Mechanical ventilation procedures

Table 6. Weaning Protocols

Author Year Country Research Design Score Sample Size	Methods	Outcome
Fenton et al. 2016 USA RCT PEDro = 6 Level 1b N = 33	**Population:** 33 patients with cervical SCI on MV (25M, 8F) Mean (SD) age: 33.1 (11.7) years. **Treatment:** control – standard MV V_T (10 ml/kg); experimental – higher ventilation V_T (20 ml/kg). **Outcome Measures:** Days to ventilator weaning, FVC, peak inspiratory pressure (PIP); plateau pressure, pulmonary adverse events, and Borg scale.	1. No significant between group difference in number of days for ventilation weaning, even after controlling for age. 2. No significant between group difference in increase of FVC. 3. Significant between group difference in increase of PIP and plateau pressure each day.

Gundogdu et al. 2017 Turkey Case control Level 3 N = 35	**Population:** 35 patients with cervical SCI with MV and/or TOT tube for a prolonged period (defined as the need for ≥ 21 consecutive days); 28 males and 7 females; mean (SD) age 29.2 (± 12.1) years; high tetraplegia (n = 7) and low tetraplegia (n = 28). **Intervention:** Implementation of a respiratory rehabilitation protocol, consisting in respiratory assessment (nutritional, cough strength, diaphragm, dysphagia and aspiration, and red flags periodic assessments), and in respiratory management (clearance of airway secretions, ventilator muscle training, MV weaning, swallowing therapy, TOT decannulation and discharge planning and vaccination). Patients were retrospectively divided in two groups (with periods from 3 to 12 weeks): ● MV-dependent patients (n = 10) underwent respiratory rehabilitation, MV weaning and a TT decannulation program. ● Tracheostomized patients (n = 25) underwent respiratory rehabilitation and a TT decannulation program. **Outcome Measures:** Diaphragmatic (chest X-ray, conduction study, needle EMG and fluoroscopy), respiratory (mean MIP, mean MEP, mean peak cough flow [PCF]) and swallowing (mean bedside dysphagia screening test, mean flexible fiber optic endoscopic evaluation of swallowing, total dysphagia, weaning time, TT decannulation time, weaned from MV, decannulated completion) evaluation.	1. MIP, MEP, and PCF values of MV-dependent patients before/after the weaning protocol were significantly improved ($p = 0.005$, $p = 0.005$ and $p = 0.012$, respectively). Pre/post treatment PCF values were also significantly improved in tracheostomized patients ($p < 0.001$). 2. 70% of MV-dependent patients were successfully weaned from MV and TT, and TOT closure was possible in 96% of the cases. In total, 85.7% of patients were decannulated. The mean duration of weaning from MV and TT decannulation were 37.0 ± 11.6 and 31.7 ± 16.9 days, respectively.
Toki et al. 2021 Japan Retrospective case series Level 4 N = 14	**Population:** 14 patients with SCI and ASIA A; 13 males and one female; mean age 28.1 years; level of injury C1 (n = 8), C2 (n = 5), and C3 (n = 1); and referred for switching their mechanical respiratory systems from TOT ventilation to NIV.	1. 11 patients were switched to NIV during hospitalization. 2. History of TOT ventilation of <1 year correlated with successful switching (100%), compared with TOT ventilation of ≥1 year (57%, $P < 0.05$). The use of NIV did not cause

	Treatment: Protocol of NIV which assess ventilator setting, interface, and respiratory training in 5 steps. **Outcome Measures:** Respiratory function tests were measured before and after NIV (VC, maximal insufflation capacity, glossopharyngeal breathing [GPB] maximum single breath capacity, and CPF). Patients who were successfully switched to NIV underwent physical examination and respiratory function tests (clinical neurological status, post-discharge complications, ventilator-free tolerance, and social status) more than 2 years (11 to 71 months) after discharge from the hospital.	major clinical complications during a period of 2 years. 3. The reasons for failure of NIV in the remaining (n = 3) patients were an episode of loss of consciousness during NIV step 4 protocol, concerning about change in lifestyle and fear of difficulty in expectoration, and the advice against the use of NIV of family physician.
Kaufman et al. 2022 USA Pre – post Level 4 N = 10	**Population:** 10 patients with ventilator-dependent cervical tetraplegia and ASIA A, 7 males and 3 females, mean age 28 (16-47) years, average time from injury 17 (1 – 48) months, and failed prior attempts at NIV and weaning protocols. **Intervention:** The treatment protocol included a surgical algorithm that involved DP, phrenic nerve reconstruction, and diaphragm muscle replacement. Treatment selection was based upon the extent of neuromuscular dysfunction, prior failed attempts at pacemaker implantation, and duration of paralysis: • Group I - Pacemaker alone (n = 2). • Group II - Pacemaker + phrenic nerve reconstruction (n = 6). • Group III - Pacemaker + diaphragm muscle replacement (n = 2). **Outcomes measures:** Time from surgery to observed reduction in ventilator requirements (↓VR), specific ventilatory needs as of most recent follow-up [no change (NC), partial weaning (PW = 1–12 h/day without MV), or complete weaning (CW ≥ 12 h/day without MV)], and complications.	1. PW (4/10) or CW (4/10) was achieved in 80% of patients whereas the remaining two patients (Group II) have demonstrated ↓VR without weaning (NC) as of the most recent follow-up (<1 year). 2. The mean duration from surgery to observed ↓VR was 4 months, and the overall mean follow-up was 23 months (range = 6–58 months). 3. Complications consisted of one patient who developed post-operative mucous plugging managed conservatively, and three patients who required pacemaker lead or receiver replacement due to malposition or malfunction.

Romero-Ganuza et al. 2015 Spain Retrospective Review Level 4 N = 228	**Population:** 228 patients with SCI Group 1: acute phase patients from ICU with respiratory failure (N=68; 49M 19F); mean age (SD): 53.8(16.6); AIS-A/B/C/D: 42/13/10/3; cervical/thoracic: 55/13; traumatic/nontraumatic: 40/28 Group 2: patients from community with respiratory complications or scheduled follow-ups (N=160). **Treatment:** MV. **Outcome Measures:** Institutionalization status, duration of MV, length of stay.	1. At discharge* of acute phase patients: 20 with permanent MV, 23/26 succeeded in weaning after a mean of 47.3(49.3) days, 13/22 already weaned patients received TOT closure, 5 expired; mean length of stay 195.6(110.4) days. 2. At discharge* of patients with complications: 9 patients admitted with MV, 6 weaned after a mean of 17.2(19.3) days; mean length of stay 53.1(56.3) days. 3. MV patients significantly more likely to be institutionalized after discharge* *discharge from intensive respiratory care unit (IRCU)
Wong et al. 2012 USA Case series Level 4 N = 24	**Population:** 24 participants with high cervical (C1-4) SCI (22M 2F); mean(SD) age: 33.4(16.6); DOI before transfer to SCI specialty unit (and start of treatment): 33.8(24.4) days. **Treatment:** High Tidal Volume Ventilation (HVtV) treatment; High Frequency Percussive Ventilation (HFPV) treatment; and Mechanical Insufflation-Exsufflation (MIE) treatment. **Outcome measures:** V_T; days before being weaned to room air; peak inspiratory pressure (PIP); plateau pressure (Pplat).	1. The respiratory status of all the study patients improved with the specialized respiratory management administered in the SCI specialty unit. For most of these patients, respiratory improvements were noted within 1 week of admission to the SCI unit. 2. Tidal volume for all patients was stabilized at 12-15mL/kg ideal body weight (mean (SD) V_T = 1037.5 (140.8)). 3. Nine (37.5%) patients were weaned to room air in ≤7 days, and another 5 patients were weaned to room air in ≤14 days. The average time for 23 out of the 24 participants to be weaned to room air was 16.3 days (*SD* 20.8). 4. 23 (96%) patients were transitioned to portable ventilators (average time 7.7 days post admission SD 5.0). 5. 14 patients were weaned from the ventilator (average time 27.6 days post admission SD 12.9 days).
Onders et al. 2010 USA Case series Level 4 N = 20	**Population:** N=20 people with SCI (17M 3F); 16-61 years old; all with internal cardiac pacemakers; all tetraplegia; 0.5-24 YPI. **Treatment:** Implantation of DP electrodes.	1. There were no peri-operative complications in any patients, nor device-to-device interactions in 19/20 patients. 2. There was device-to-device interaction in 1 patient, which was

	Outcome Measures: Hours of daily use of DP, implantation, negative interactions between cardiac pacemaker and DP (device-to-device interaction), conditioning, ability to wean from MV.	resolved by disabling the interacting electrode in question. 3. All patients achieved diaphragm paced V_T necessary to meet their basal metabolic needs. 14/20 patients finished conditioning with their diaphragm and reached their maximal goal. 4. Ten of the above 14 use DP 24 hours a day with no MV. 5. Three other patients use DP 8-12 hours during the day, with 1 reaching a maximum of 4 hours by choice. 6. The remaining 5 participants (excluding the early death), were still increasing their DP sessions through conditioning at the end of the study.
Gutierrez et al. 2003 USA Pre-post Level 4 N = 7	**Population:** 7 tetraplegia: C2(n=2), C4-C7(n=5), incomplete, all male, age range: 45-68 years, time on ventilator: 4-36 months. **Treatment:** Implementation of an evidence-based resistive endurance protocol designed to help discontinue MV by improving ventilatory muscle strength and endurance. **Outcome Measures:** Pulmonary function tests; on-ventilator endurance and off-ventilator endurance.	1. Participants with low tetraplegia achieved significant gains in inspiratory & and expiratory muscle strength, VC, mean on-ventilator endurance & off-ventilator endurance. 2. Participants with high tetraplegia had non-significant improvements in inspiratory and expiratory muscle strength and VC and were able to discontinue MV. 3. 4/5 participants with low tetraplegia were weaned from the ventilator. 1/5 low tetraplegic participants died.
Peterson et al. 1994 USA Case Series Level 4 N = 52	**Population:** Tetraplegia (C3-C4), ventilator dependent. **Treatment:** Retrospective review of 82 ventilator weaning attempts in 52 participants using intermittent mandatory ventilation (IMV), progressive ventilator free breathing (PVFB) or a combination of other ventilator weaning techniques. **Outcome Measures:** Successful ventilator weaning.	1. 26/82 weaning attempts used IMV, 34/82 used PVFB and 22/82 used a combination of various techniques. 2. PVFB weaning success rate was 67.6 % (23/34) and IMV was 34.6% (9/26) and other techniques was 11/22. 3. Overall 43/52 (83%) of participants were successfully weaned. 6/52 were partially weaned. 2/52 participants died.

Discussion

The systematic review of Schreiber et al. (2021) included 39 studies (with 14637 patients, of which 874 were in rehabilitation units) and found that in addition to high-level lesions, multiple comorbidities, a high Injury Severity Score, elevated heart rate, and presence of TOT were also associated with increased odds of weaning failure. Furthermore, shorter time to admission to a specialized SCI center, complete lesions, presence of TOT, low V_T, and high positive end-expiratory pressure were associated with a longer duration of MV (Schreiber et al. 2021). They also found that 72-82% of the patients admitted to a rehabilitative ward were either completely or partially liberated from the ventilator, 35.5% (11.3 – 70.5%) developed pneumonia, and less than 1% (0 – 18.5%) died (Schreiber et al. 2021).

Peterson et al. (1994) retrospectively compared weaning methods in people with C3-C4 SCI. Overall 83% of participants were successfully weaned with PVFB (also known as T-piece weaning) being the most successful technique.

Gutierrez et al. (2003) developed an evidence based resistive and endurance protocol to improve ventilatory muscle strength and endurance in people with ventilator-dependent cervical SCI. The protocol included 4 daily phases with rests between each phase: pre-training optimization (Trendelenburg positioning, trachea suctioning, bronchodilator use, and lung hyperinflation); inspiratory/expiratory resistive training; on-ventilator endurance training; and off-ventilator endurance training. Although the pilot study only included 7 participants, it showed promising results with respect to increasing inspiratory pressure, expiratory pressure and VC, and ultimately ventilator weaning, especially in people with low tetraplegia (C4-C7) (Gutierrez et al. 2003).

Onders et al. (2010) evaluated diaphragm pacing (DP) as a weaning method in 20 participants who also had cardiac pacemakers and found no immediate or long-term device-to-device interactions. All patients could go >4 hours without mechanical ventilators, and 71% could go 24 hours continuously with DP.

Wong et al. (2012) retrospectively analyzed the charts of 24 people with high cervical SCI (C1-C4) who underwent high tidal volume ventilation (HVtV) treatment, high frequency percussive ventilation (HFPV) treatment and/or and mechanical insufflation-exsufflation (MIE) treatment in a specialized SCI treatment unit. All patients showed improvements in their respiratory status and 14 patients were successfully weaned from their ventilators.

Gundogdu et al. (2017) retrospectively analyzed 35 participants with cervical SCI with MV and/or TOT tube for a prolonged period. MV-dependent patients who underwent respiratory rehabilitation, MV weaning, and a TT decannulation program, showed an improvement in some respiratory parameters (MIP, MEP and peak cough flow [PCF]) and a rate of 70% of successful weaning from MV and TT, while tracheostomized patients who underwent respiratory rehabilitation and a TT decannulation program showed an increase in PCF and a rate of 92% of successful on decannulation. The mean duration of weaning from MV and TT decannulation was 37.0 ± 11.6 and 31.7 ± 16.9 days, respectively.

Kaufman et al. (2022) prospectively studied a treatment protocol using a surgical algorithm involving DP, phrenic nerve reconstruction, and diaphragm muscle replacement. They analyzed 10 patients with ventilator-dependent cervical tetraplegia and ASIA A, who received different treatments based on the extent of neuromuscular dysfunction (pacemaker alone, pacemaker +

phrenic nerve reconstruction or pacemaker + diaphragm muscle replacement), showing 4 patients who achieved a partial and 4 a complete weaning.

Toki et al. (2021) retrospectively analyzed 14 patients with TOT, SCI, and ASIA A who received a protocol of non-invasive ventilation (NIV) which assessed ventilator setting, interface, and respiratory training. 11 patients were switched to NIV, showing that a history of TOT ventilation of less than one year was correlated with successful switching (100%), compared with TOT ventilation of ≥ 1 year.

Prospective studies on weaning protocols are required to determine the best way to assess, treat and wean people requiring MV following SCI.

Mechanical insufflation-exsufflation (e.g., using a "Cough Assist machine") is a therapy in which the device gradually inflates the lungs (insufflation), followed by an immediate and abrupt change to negative pressure, which produces a rapid exhalation (exsufflation), which simulates a cough, and helps to clear secretions.

Conclusion

There is level 4 evidence (from one case series Wong et al. 2012) that the implementation of specialized respiratory management (HVtV, HFPV, MIE) resulted in an improvement of respiratory status in all study participants.

There is level 3 evidence (from one retrospective study: Gundogdu et al. 2017) that the implementation of a respiratory rehabilitation protocol, consisting of respiratory assessment and management of different aspects, improved respiratory parameters of MV-dependent patients before/after the weaning protocol and also in tracheostomized participants; provided a rate of 70% of successful weaning from MV ant TT in MV-dependent patients, a rate of 96% of TOT closure and a rate of 85.7% of decannulation in patients with cervical SCI.

There is level 4 evidence (from one prospective study: Kaufman et al. 2022) that the implementation of a treatment protocol which included a surgical algorithm that involved DP, phrenic nerve reconstruction, and diaphragm muscle replacement provided a rate of 80% of successful weaning (40% partial weaning and 80% complete weaning) in patients with ventilator-dependent cervical tetraplegia and ASIA A.

There is level 4 evidence (from one retrospective study: Toki et al. 2021) that the implementation of a protocol of NIV which assess ventilator setting, interface, and respiratory training in 5 steps provided a rate of 78.6% of a successful switch to NIV in patients with SCI and ASIA A.

There is level 4 evidence (from one case series study: Peterson et al. 1994) that PFVB protocol is more successful for weaning people with C3 and C4 spinal cord injuries than IMV.

There is level 4 evidence (from one case series study: Onders et al. 2010) that DP served as an effective weaning protocol in all participants.

There is level 4 evidence (from one pre-post study: Gutierrez et al. 2003) that a resistive and endurance protocol increases inspiratory pressure, expiratory pressure, and VC especially in low tetraplegia (C4-C7).

There is level 4 evidence (from one retrospective case series: Romero-Ganuza et al. 2015) that though many people with SCI will require MV they can be successfully weaned from it.

Key Points

PVFB protocol should be considered for ventilator dependent people with tetraplegia who are appropriate for ventilator weaning.

Resistive and endurance training should be considered in people who are candidates for ventilator weaning.

8 Tracheostomy (TOT) Decannulation

Evidence for the decannulation of people with SCI is lacking. People may not meet the traditional criteria for decannulation and should be assessed on an individual basis (Bach & Alba 1990; Ross & White 2003).

Table 7. Tracheostomy (TOT) Decannulation

Author Year Country Research Design Score Sample Size	Methods	Outcome
Kim et al. 2017a Korea Case series Level 4 N = 62	**Population:** 62 patients with cervical SCI who had received invasive acute phase respiratory management and succeed in either decannulation or extubation, mean (SD) duration from TOT to decannulation 7.0 (± 14.5) months); 55 males and 7 females; mean (SD) onset age 47.6 (± 15.8) years; ASIA A (n = 49) and ASIA B (n = 13); neurological level C- (n = 1), C1 (n =	1. Of the 62 patients: a. 25/62 achieved transition to NIV after extubation/decannulation. b. 16/62 achieved ventilator weaning after extubation / decannulation. c. 2/62 were TOT MV with re-tracheostomy after decannulation. d. 12/62 had simple decannulation without applying long-term MV.

	3), C2 (n = 9), C3 (n = 23), C4 (n = 20), C5 (n = 2), C6 (n = 2), C7 (n = 0), and C8 (n = 2). **Intervention**: Invasive acute phase respiratory management (including mechanically assisted coughing and NIV) for patients with TOT (n = 60) and endotracheal intubation (n = 2). **Outcome Measures:** Medical charts (including discharge summaries), imaging studies, and detailed pulmonary function test results (FVC in sitting and supine position, MIP, MEP, and unassisted and assisted PCF assessed just before each patient's decannulation) were collected before initial admission and after the intervention (mean (SD) follow-up period 21.3 (± 29.8) months).	e. 7/62 were applied of NIV after decannulation. 2. For those who switched to NIV (n = 31), hours of daily need for ventilatory support gradually decreased to 5.7 ± 5.7 h at final discharge.
Kang et al. 2016 Korea Pre – post Level 4 N = 16	**Population:** 16 patients with neuromuscular diseases (n = 11) and SCI (n = 5) who were tracheostomized and did not satisfy the criterion for decannulation (an assisted peak cough flow [APCF] of 160L/min). Patients with comprised 5 males, mean age 45 years, ASIA A (n = 3) and ASIA C (n = 2). **Intervention:** Unassisted peak cough flow (UPCF) and APCF were measured with and without an external glottic control device. Among patients whose APCF without the device was <160L/min, if their APCF with the device was measured as ≥160L/min, they were decannulated. **Outcome measures:** APCF with and without an external glottic control device as well as UPCF and APCF after decannulation.	1. Before decannulation, APCF with an external control device was 207 L/min, which was higher than APCF without the device in all patients. 2. None of patients suffered from respiratory complications or rehospitalization during the research period. 3. After decannulation, 2 of 4 patients who had required additional ventilator support during waking hours used the ventilator during sleep time only and 1 patient required less time for using the ventilator after decannulation. 4. In all patients, APCF was > 160 L/min after decannulation, and the average APCF was 302 L/min; which was significantly higher than the average APCF with an external control device before decannulation (P = 0.002). 5. An external control device substituting for glottic function is beneficial for determining TOT decannulation because it provides an objective and accurate measurement of APCF. Therefore, this device is helpful, particularly in patients whose APCF is ≥160L/min

		while using the device, even if APCF is <160L/min without this device.
Ross & White 2003 Australia Case series Level 4 N = 4	**Population:** tetraplegia (n=3) and paraplegia (n=1), level: C5-T9, AIS A (n=3) & B(n=1), age: 20-71 yrs. **Treatment:** Interdisciplinary evaluation and assessment. **Outcome Measures:** Successful decannulation.	1. 4 participants who had evidence of aspiration were successfully decannulated after assessment by a multidisciplinary team. 2. None experienced respiratory deterioration.

Discussion

Kim et al. (2017a) retrospectively studied 62 patients with complete or sensory incomplete cervical SCI who received an invasive acute phase respiratory management (including mechanically assisted coughing and NIV). They found that TOT decannulation was possible and noninvasive respiratory intervention, including NIV and mechanically assisted coughing, was an effective long-term alternative to TOT.

Kang et al. (2016) conducted a pre-post design on 16 patients with neuromuscular diseases (5 patients with SCI) who were tracheostomized and did not satisfy the criterion for decannulation. They tested on an objective criterion for decannulation using an external control device substituting for glottic function among patients whose assisted peak cough flow (APCF) without the device was <160L/min. If their APCF with the device was measured as ≥160L/min, they were decannulated. This objective and accurate measurement of APCF was shown to be beneficial in determining TOT decannulation, particularly in patients whose APCF was ≥160L/min while using the device, even if APCF was <160L/min without this device.

Ross and White (2003) described a case series of 4 people with SCI who were successfully decannulated despite the presence of traditional contraindications for decannulation such as evidence of aspiration. These 4 people were carefully selected by a multidisciplinary team who opted for decannulation after assessing the overall risks of decannulation vs. the risks of prolonged TOT. Further studies examining the criteria for decannulation of people with SCI are required.

Conclusion

There is level 4 evidence (from one case series study: Kim et al. 2017a) that an invasive acute phase respiratory management (including mechanically assisted coughing and NIV) for patients with cervical SCI receiving TOT or endotracheal intubation provides successful in TOT decannulation; and noninvasive respiratory intervention, including NIV and mechanically assisted coughing, is an effective long-term alternative to TOT.

There is level 4 evidence (from one pre-post study: Kang et al. 2016) that specific criteria and device (external control device substituting for glottic function) used for decannulation which consists of decannulate patients whose APCF without the device was <160L/min, and their APCF with the device was measured as ≥160L/min, is beneficial for determining TOT decannulation in patients with neuromuscular diseases, including patients with SCI.

There is level 4 evidence (from one case series study: Ross & White 2003) that decannulation can be successful in people with evidence of aspiration.

Key Points

There is some evidence that the implementation of an invasive acute phase respiratory management for patients with cervical SCI receiving TOT or endotracheal intubation is successful in TOT decannulation.

There is some evidence that a specific criteria; which consists of decannulating patients whose APCF without an external control device substituting for glottic function was <160L/min and their APCF with the device was measured as 160L/min; is beneficial for determining TOT decannulation in patients with neuromuscular diseases, including patients with SCI.

The indications and criteria for TOT decannulation have not been well established in SCI. Until more evidence is available, case by case consideration should be given to TOT decannulation in people with SCI.

9 Exercise Training of the Upper and Lower Limbs

As with people without SCI, there is strong evidence in support for the use of exercise training for improving cardiovascular health among people with SCI (see Cardiovascular Heath and Exercise module). This is important because there is a high incidence of physical inactivity in people with SCI and as such, they are at increased risk of secondary conditions such as cardiovascular disease, diabetes, osteoporosis, and obesity. There is clear evidence that the cardiovascular and skeletal muscle systems adapt positively to exercise training in with or without SCI. However, the lungs and airways do not change appreciably in response to exercise training. It is likely that exercise is not sufficiently stressful to warrant an adaptive response. This may be even more so when considering the small muscle mass used in wheelchair propulsion or arm cranking exercise. On the other hand, respiratory muscles are both metabolically and structurally plastic and they respond to exercise training. This statement is based largely on direct evidence from animal models and indirect evidence from able-bodied humans.

Exercise training may influence the control of breathing and respiratory sensations (i.e., dyspnea). It is generally accepted that exercise training results in a lower V_E at any given absolute oxygen consumption or power output. This is likely due to a reduction in one or more of the mechanisms (neural and/or humoral) purported to cause the hyperpnea (increased respiratory rate) associated with exercise. As such, the positive effects of exercise training in SCI may reside in an increase in respiratory muscle strength and endurance as well as a reduced ventilatory demand during exercise. A lower ventilation and/or sensation of dyspnea during exercise would lower the work of breathing and prevent early termination of exercise, respectively.

Table 8. Exercise Training of the Upper and Lower Limbs

Author Year Country Research Design Score Sample Size	Methods	Outcome
Xiang et al. 2021; China RCT (pilot) PEDro = 8 Level 1 N = 18	**Population:** 18 patients with SCI; 15 males and 3 females; mean age 38.2 years; AIS A (n = 12), AIS B (n = 2), and AIS C (n = 4); level of injury T4-T10 (n = 9) and T11-below (n = 9); and median duration of injury 2 months. **Treatment:** The participants were divided into exoskeleton-assisted walking (EAW) group (n = 9) or conventional group (n = 9). Intensity, duration, and frequency were similar in both groups (40–60% HRmax, 50–60 min/session, 4 days/week, 4 weeks): ● EAW group: Training session included sitting, standing, walking, climbing stairs and slope. ● Conventional group: Consisted in strength training using dumbbell, aerobic exercise, such as walking training with brace as well as static and dynamic balance training. **Outcome Measures:** Pulmonary function test (FVC, predicted FEV%, FEV_1, $FEF_{25/50/75}$, PEF, and MVV), 6-MWT, HR, SpO_2, RPE, LEMS, and ASIA scores were collected and analyzed pre and post intervention.	1. There were no adverse events. 2. FVC (t = 2.224; p = 0.041), predicted FVC% (t = 2.848, p = 0.012) and FEV_1 (t = 2.779; p = 0.013) showed significant improvements for EAW group vs. conventional group. 3. EAW group had statistical improvements from pre- to post-intervention in mean change in predicted FVC% (Δ = 17.2%; t = 2.445; p = 0.040), FEV_1 (Δ = 0.8 L; t = 3.359; p = 0.010), FEF_{75} (Δ = 1.7 L/s; t = 3.268; p = 0.011), PEF (Δ = 1.8 L/s; t = 3.381; p = 0.010), and MVV (Δ = 19.3 L; t = 3.274; p = 0.017). EAW training produced no statistical improvements in distance and SpO_2 vs. conventional group during 6-MWT. 4. There was no evidence of statistical improvements from pre- to post- intervention in conventional group in FVC, predicted FVC%, FEV_1, FEF_{75}, FEF_{50}, FEF_{25}, PEF, and MVV. There were also no statistical differences for the conventional group in distance, HR, SpO_2, and RPE.
Vivodtzed et al. 2020a USA RCT (crossover) PEDro = 7 Level 1 N = 19	**Population:** 19 patients with SCI, wheelchair-dependent who needed FES to produce leg contractions for exercise, all had been training with FES-rowing for at least 6 months; mean (SD) age 39 (± 13) years; mean time since injury 9.05 years; level of injury ranged from C4 to T8; and AIS A (n = 8), AIS A/B (n = 1), AIS B (n = 3) and AIS C (n = 7). **Treatment:** Two hybrid FES-rowing peak exercise tests (performed with NIV or sham in random order). **Outcome Measures:** Changes in peak alveolar ventilation (VApeak) and peak oxygen consumption (VO_2peak) during	1. NIV significantly changed respiratory pattern. Patients breathed deeper and slower with NIV compared with the sham (P < 0.05). As a result, VApeak was not changed on average with NIV; the change in VApeak was related to the change in V_T (r = 0.89; P < 0.01) but not to the change in fB (r = 0.20; P = 0.51). 2. Average VO_2peak (n = 13) did not change with NIV vs. sham. However, there was a strong correlation between change in

	the incremental FES-rowing test (n = 13 met criteria for peak exercise), oxygen uptake efficiency slope (OUES) (a nonlinear measure of the ventilatory response to exercise, as an index of cardiopulmonary reserve for patients who didn't meet criteria for peak exercise, n = 6)), changes in respiratory pattern (peak V_T] and peak breathing frequency [fb]) during exercise testing.	VApeak (NIV – sham) and change in VO_2peak (r = 0.89; P < 0.05). 3. OUES (n = 19) was not improved. Moreover, change in VApeak was a discriminant factor for change in OUES; those in whom NIV increased VA (6 ± 3 L; n = 12) demonstrated an approximately 50% improvement in OUES, whereas those in whom NIV did not increase VA (–6 ± 6 L; n = 7) demonstrated an approximately 5% reduction in OUES (P < .05). 4. Those with TSI ≤ 6 years increased OUES with NIV significantly more than participants with TSI > 6 years (0.89 ± 1.59 [n = 12] vs. –0.59 ± 0.84 [n = 7]; P < 0.05). Moreover, there was a tendency for OUES to increase in those with cervical injuries compared with those with thoracic injuries (0.79 ± 1.79 [n = 12] vs. –0.37 ± 0.39 [n = 7]; P = 0.15). 5. Lastly, those with incomplete injury tended to have greater improvements in VO_2peak than those with complete injury (P = 0.11).
Vivodtzed et al. 2020b USA RCT PEDro = 3 Level 2 N = 9	**Population:** 9 people with high-level SCI (T3-C4) who had been participating in a rehabilitation program training with whole-body hybrid FES-rowing during 4 ± 2 years, and having training adaptations plateauing for more than 6 months; mean age 38.9 years; mean time since injury 13.1 years; level C4 (n = 3), C5 (n = 1), C6 (n = 1), C7 (n = 1), T2 (n = 1), and T3 (n = 1); AIS A (n = 4), AIS B (n = 1), and AIS C (n = 4). **Treatment:** Patients had completed the study of Vivodtzed et al. 2020a (see above) and continue with whole-body hybrid FES-rowing training for 3 months with NIV (n = 6: IPAP = 20 ± 2, EPAP: 3 cmH_2O) or sham (n = 3: IPAP = 5, EPAP: 3 cmH_2O). **Outcome Measures:** Aerobic efficiency (OUES) was collected at baseline (sham condition) and after 3 months of training (test in NIV and sham condition) performing maximal exercise tests.	1. Training with NIV increased OUES both compared to baseline (4.1 ± 1.1 vs. 3.4 ± 1.0, p < 0.05) and sham (p = 0.01) while no change was found in sham (1.8 ± 0.3 vs. 2.1 ± 0.8, after vs. before respectively. This result was found without NIV during the final test. Adding NIV during the final test did not provide additional improvement in OUES (4.1 ± 1.5 and 2.0 ± 0.7, in NIV and Sham respectively). 2. In participants with reliable measures of VO_2peak, a homogeneous improvement was also found in VO_2peak in those using NIV (+0.21 ± 0.04 L/min) while the response was, randomly changed in the sham group (+0.08 ± 0.10 L/min). 3. Improvement in OUES was associated with an overall reduction in peak breathing

		frequency after training with NIV while it tended to increase with Sham (− 3 ± 6 [range: from 33 to 52 to 30–38 bpm] vs. +4 ± 8 [range: from 33 to 46 to 35–51 bpm], p = 0.19). 4. $V_T$peak unchanged in both groups. 5. Peak SpO2 ranged between 94% and 99% without differences between groups, but there was a slight drop in VD/VT in the NIV group from 0.24 ± 0.09 to 0.22 ± 0.06 which was not found in the sham group, suggesting improvement in OUES was related to improved alveolar ventilation rather than change in O_2 delivery.
Mat Rosly et al. 2017 Malaysia Cohort Level 2 N = 17	**Population:** 17 participants with SCI; 16 males and one female; mean age 35.6 (± 10.2) years; neurological level of injury T4 and above (n = 4) and T5 and below (n = 13); AIS A (n = 11), AIS B (n = 3), AIS C (n = 2) and AIS D (n = 1); and mean (SD) time since injury 14.1 (± 5.6) years. **Intervention:** Participants performed, in a randomized order, two different boxing sessions of 15 minute (set at a minimum of 2 days and maximum of 14 days apart). Modalities consisted in: ● Exergaming boxing: The game was projected and run by a video game console with two controllers and a sensor camera. ● Conventional heavy-bag boxing: Utilized a 1.65-m, 35-kg punching bag hung in suspension. **Outcome measures:** Heart rate (HR), resting HR, VO_2, energy expenditure (EE), total energy expenditure, V_E, metabolic equivalent (MET), RPE (0-10), and self-constructed survey were collected at before and during the exercise sessions.	1. Both exergaming and heavy-bag boxing achieved moderate intensities of exercise with 4.3 ± 1.0 MET and 4.4 ± 1.0 MET being achieved, respectively. 2. No significant differences in the physiological or perceived exertional responses between boxing modalities were found. 3. There was a significant preference (P<0.05) for exergaming boxing over heavy-bag boxing among responses in the self-constructed survey.
Chen et al. 2016 China RCT PEDro = 4 Level 2 N = 98	**Population:** 98 males with traumatic SCI paraplegia; C5-C7; mean (SD) age 62.7 (± 10.8) years; mean (SD) time since injury 41.6 (± 10.8) years; and injury level T1-T2 (n = 39), T3-T4 (n = 32), and T5-T6 (n = 32). **Intervention:** Participants were divided in two groups:	1. The data analyses for 2 months, 4 months and 12 months displayed highly significant differences in pulmonary function and life-quality (P < 0.01) between experi-mental group and control group. 2. There was no difference (P > 0.05) one month after pulmonary

	• Experimental group (n = 49) acquired pulmonary rehabilitation exercise for 12 months, consisting in breath training and strength training. Strength training consisted in 20 min and one time a day session, with an expected 75-85% of maximum HR. • Control group (n = 49). All patients acquired conventional rehabilitation, including psychological rehabilitation and dietary guidance. **Outcome measures:** Pulmonary function (FEV_1, FVC, MVV) and FEV_1/FVC) and QOL (SF-36) were detected at baseline; during pulmonary rehabilitation at 2 months, 4 months, and 12 months; and 1 month after pulmonary rehabilitation.	rehabilitation between experimental group and control group.
Soriano et al. 2022 Croatia Pre-post Level 4 N = 11	**Population:** 11 people with a traumatic cervical SCI; 7 males and 4 females; mean (SD) age 40 (± 10) years; mean (SD) time since injury 17.73 (± 9.40) years; level of injury C3 (n = 1), C4 (n = 1), C5 (n = 5), C6 (n = 3), and C7 (n = 1); AIS A (n = 5), AIS B (n = 4), and AIS C (n = 2). **Treatment:** A single session of passive leg cycling in supine, performed for 10 min at 29 ± 1 rpm using a motorized cycle. **Outcome Measures:** Beat-by-beat arterial blood pressure, heart rate (HR), stroke volume and cardiac contractility, blood velocity of the right middle cerebral artery and left posterior cerebral artery, V_E, V_T, end-tidal fractional concentration of O_2 and CO_2, mean arterial pressure, mean velocity in the MCA and PCA, cardiac output, total peripheral resistance, cerebrovascular conductance, femoral artery diameter and function, blood velocity, flow-mediated dilation, and safety.	1. V_E (0.67 ± 0.23 L/min, p = 0.008), V_T (70 ± 30 mL, p = 0.008), and end-tidal PO_2 (2.6 ± 1.23 mm Hg; p = 0.030) were increased. 2. There were no exertional hypotension or major adverse effects except for one patient who suffered an episode of autonomic dysreflexia and was excluded of the analysis.
Leathem et al. 2021 USA Pre-post Level 4 N = 6	**Population:** 6 participants with SCI; 5 males and 1 female; incomplete injury (n = 4) and complete injury (n = 2); cervical injury (n = 4) and thoracic injury (n = 2); mean (SD) age 33 (± 18.6) years; and mean (SD) time since injury 7 (± 4) years. **Treatment:** Treatment consisted in two modalities: • Spinal Mobility X class: Performed once per week for 8 consecutive weeks. Each four-hour class was comprised of three circuits:	1. None of the participants reported adverse effects due to the respiratory training; and subjects reported various improvements in the surveys. 2. Mean difference for all measures across participants indicates overall improvement in all four functional outcome measures.

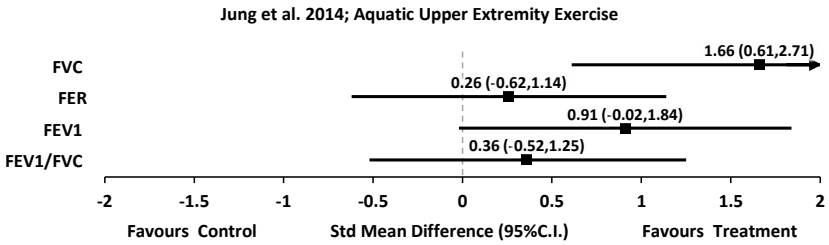
	strengthening, aerobic training, and spinal mobility. ● IMT as a home exercise program. **Outcome Measures:** Subjective survey, transfer test, t-shirt test, four directional reach test, and four-directional trunk test were collected before and after the program.	
Brizuela et al. 2020 Spain Pre-post Level 4 N = 11	**Population:** 11 participants with traumatic cervical SCI; 8 males and 3 females; mean (SD) age 36.5 (± 10) years; AIS A (n = 8) and AIS B (n = 3); injury level C4 (n = 1), C5 (n = 5), C6 (n = 2), and C7 (n = 3). **Treatment:** Participants were divided in two groups: ● Higher CSCI (C4-C5) (n = 6). ● Lower CSCI (C6-C7) (n = 5). They performed a stationary armcrank exercise for 8 weeks, twice a week. Exercise duration augmented progressively each 2 weeks until reach 30-40 min at the end of the program. Constant cadence and resistance were set individually with the aim of maintain a RPE (Borg scale) between 2-3/10 (light to moderate) during training sessions. **Outcome Measures:** Quadriplegia index of function questionnaire, Arm-crank power output (Ppeak), heart rate variability, and spirometric variables (VC, FVC and MVV) were measured before and after the training program.	1. VC and FVC showed a slight but non-significant tendency (p = 0.14 and p = 0.17, respectively) to increase after the ACE program. 2. All functional and pulmonary variables showed significant differences between levels of injury, with higher values for participants with lower-level CSCI.
Panza et al. 2019 USA Pre-post Level 4 N = 3	**Population:** 3 male patients with incomplete SCI; mean (SD) age 25.33 (± 8.74) years; AIS C (n = 3); C4 (n = 1) and C5 (n = 2); and mean (SD) time since injury 39.0 (± 19.97) months. **Treatment:** Overground locomotor training (OLT) (training used part-to-whole-practice sequences based on the task-specific movements in the gait cycle, and containing five consecutive training segments: joint mobility, volitional muscle activation, task isolation, task-integration, and activity rehearsal). Participants used only volitional control and training was conducted without body-weight support, robotic devices, or ES. Sessions lasted 90 min and were conducted twice a week for 12 weeks.	1. As a group (n = 3), there was a 2% increase in V_E and a 9% decrease in V_T. Neither V_E (d = 0.1) or V_T (d = 0.4) during rest demonstrated a large effect size. 2. The phasic response to exercise improved (became faster) following OLT. 3. Data showed medium to large reductions in V_E variability (24%), V_T variability (29%), estimated work of breathing, VCO_2 and $P_{ET}CO_2$, and RPE (30%) following OLT.

	Outcome Measures: Weight, cardiorespiratory variables (VO_2, VCO_2, V_E, V_T, and end-tidal partial pressure of CO_2 [$P_{ET}CO_2$]), work of breathing, and RPE. Testing protocol consisted in a 6-min walking bout at their individually determined preferred walking speed, 6 min rest, and the second 6 min walking bout with a self-selected faster walking speed than the first bout (analysis was performed of the second bout). Testing protocol was performed before and after OLT (12 weeks) at the same speeds.	
Panza & Guccione 2020 USA Pre-post, Repeated Measures Level 4 N = 8	**Population:** 8 male patients with incomplete SCI; mean (SD) age 45 (± 16.3) years; injury level C3-C6 (n = 6), T5 (n = 1) and T12 (n = 1); and mean (SD) months since injury 44.3 (± 17.3). 8 able-bodied, 7 males and one female, mean (SD) age 34.6 (± 11.3) years. **Treatment:** OLT (training used part-to-whole-practice sequences based on the task-specific movements in the gait cycle containing five consecutive training segments: joint mobility, volitional muscle activation, task isolation, task-integration, and activity rehearsal). Participants used only volitional control and training was conducted without body-weight support, robotic devices, or ES. Sessions lasted 90 min and were conducted twice a week for 24 weeks (training period was divided in two 12-weeks cycles of OLT). **Outcome Measures:** Weight, cardioventilatory parameters (VO_2, VCO_2, V_E, V_E variability, V_T, breathing frequency [Bf]), work of breathing, and RPE. Testing protocol consisted in a 6-min walking bout at their individually determined preferred walking speed (constant work rate), 6 min rest, and then, patients had to walk at the same self-selected pace until a volitional fatigue or 30 min, whichever came first (analysis was made based on the second walking bout). Participants performed the treadmill testing protocol at baseline, at post first OLT (post 1) and post second OLT (post 2).	1. Ventilatory response to exercise is accelerated after 12 and 24 weeks of OLT, with concomitant improvements in walking endurance and reductions in RPE after 12 and 24 weeks of OLT. 2. Ventilatory variability reduced at 12 weeks, but returned to pre-OLT values after an additional 12 weeks of training despite the continued reduction in RPE and improvements in walking endurance. 3. V_E variability was correlated with the change in RPE through the study. 4. 12 and 24 weeks of OLT resulted in significant improvements in treadmill walking time.

Panza et al. 2017 USA Pre – post Level 4 N = 6	**Population:** 6 patients with incomplete SCI (AIS C); 5 males and one female; mean (SD) age 36.17 (± 19.36) years; injury level C4-C5 (n = 5) and C5 (n = 1); and between 2- and 5-years post injury. **Treatment:** OLT program performed in two 90-minute training sessions per week for 12 weeks. Each training session involved five consecutive training segments, all with a particular focus as follows: joint mobility; volitional muscle activation; task-isolation; task-integration; and activity rehearsal. Participants were required to perform all exercises under volitional control, but without the assistance of body-weight support harnesses, robotic devices, ES or orthoses and other lower-extremity supportive devices. **Outcome Measures:** Height, weight, cardiorespiratory variables (V_T, Bf, V_E and V_E variability). All participants underwent a 6-minute volitional unaided walking bout at a constant work rate on a motorized treadmill. Participants were instructed to stand quietly for 3 min, prior to walking at their preferred walking speed for 6min. The same testing procedures were repeated after 12 weeks of OLT at the same walking speed used at pre-testing.	1. The averaged group data for resting and for exercise V_E, V_T and Bf showed no difference before and after training. 2. Exercising V_E variability was significantly reduced in four of the five participants resulting in a group average reduction of 11.87 arbitrary units. The group V_E variability was reduced by 46.7% on average. These data didn't show a phasic ventilatory response to treadmill walking at preferred walking speed before or after OLT.
Gollie et al. 2017 USA Pre-post Level 4 N = 6	**Population:** 6 patients with chronic (2 to 5 years post injury), cervical incomplete SCI, 5 males and one female, age range between 19 and 67 years, 5 AIS C (n = 5) and AIS D (n = 1). **Treatment:** The OLT protocol consisted of two 90-minute training sessions per week and it was performed during 12-15 weeks. Each training session involved five consecutive training segments, all with a particular focus as follows: joint mobility; volitional muscle activation; task-isolation; task-integration; and activity rehearsal. Participants were required to perform all exercises under volitional control, but without the assistance of body-weight support harnesses, robotic devices, ES or orthoses and other lower-extremity supportive devices. **Outcome Measures:** Overground walking speed, RER, VO_2, and VCO_2, HR, and BMI were collected pretest and posttest (each testing visit consisted of a 10-m walk test	1. OLT did not result in any adverse events. 2. After training, overground walking speed was significantly increased during the 10-MWT (0.36 ± 0.20 vs. 0.5 ± 1.24m/s, P < 0.001, d = 0.68) with a range of overground walking speeds of 0.24 to 0.88m/s. 3. During constant work rate treadmill walking VO_2 was significantly lower after training than before training (6.6 ± 1.3 vs. 5.7 ± 1.4 mL·kg·min, P = 0.038, d = 0.67). Furthermore, VCO_2 was significantly reduced after OLT (753.1 ± 125.5 vs. 670.7 ± 120.3 mL/min, P = 0.036, d = 0.67). The VO_2 required above standing rest during self-selected walking was significantly greater than the estimated VO_2 both before (6.6 ± 1.3 vs. 1.9 ± 0.78 mL·kg·min, P <

	(10-MWT) and a constant work rate submaximal treadmill test while walking at a self-selected walking speed).	.05) and after training (5.7 ± 1.4 vs. 1.9 ± 0.78mL·kg·min, P < 0.05).
Gorgey & Lawrence 2016 USA Pre-post Level 4 N = 10	**Population:** 10 participants with chronic motor complete SCI (C5-T10); 9 males and 1 female; mean age 44 (± 9.5) years; and AIS A or B. **Intervention:** An acute bout of FES-lower extremity cycling (FES-LEC) until fatigue (10 ± 8 min). **Outcome Measures:** Body composition assessment (whole-body impedance analyzer at the familiarization session), V_E, VCO_2, ventilation-to-carbon dioxide (VE/VCO_2) ratio, RER and substrate utilization were measured using indirect calorimetry during resting, warm-up, exercise, and recovery phases.	1. Breathing frequency increased significantly from 15 ± 4 breaths/min during rest and 16 ± 4.5 breaths/min during warm-up periods to 18 ± 5 breaths/min during exercise (P = 0.017) and remained significantly elevated during the recovery period (18 ± 4.5 breaths/min; P = 0.049). 2. V_E significantly increased (14.5 ± 6.4 L/min; P = 0.008) and remained significantly (13.3 ± 4.3 L/min; P = 0.001) elevated during the recovery period compared with the resting period. 3. VCO_2 increased significantly from 0.18 ± 0.085 L/min during rest to 0.45 ± 0.21 L/min during exercise (P = 0.004) and remained significantly elevated during the recovery period (0.36 ± 0.12 L/min; P = 0.001). 4. Compared with resting (40.5 ± 4.5) and warm-up (38 ± 5; P = 0.055) periods, VE/VCO_2 ratio dropped significantly during FES-LEC exercise (32 ± 4; P = 0.0001) and remained depressed during the recovery (34.5 ± 3; P = 0.099) period. 5. RER did not change between resting (0.85 ± 0.06) and warm-up (0.83 ± 0.09) periods. However, it did increase significantly (P = 0.001) during exercise (1.09 ± 0.15) and remained elevated during the recovery (1.09 ± 0.06) period.
Qiu et al. 2016 USA Pre-post Level 4 N = 12	**Population:** 12 participants with SCI at T2 and above, 11 males and one female, mean (SD) age 33.3 (± 3.8) years, and mean (SD) time post-injury 8.3 (± 3.3) years. **Intervention:** FES-RT for 6 weeks, three times weekly, 30 minute each session with the goal of reaching an exercise intensity of 75%–85% of HRpeak. **Outcome Measures:** VO_2, VCO_2, RER, expired VO_2 and CO_2 gas fractions, V_E, V_T, peak aerobic capacity (VO_2peak), peak	1. Compliance to the 6-month training program averaged 1.8 ± 0.2 rowing sessions per week, corresponding to 59% of planned sessions. 2. VO_2peak increased on average by 12%, from 15.3 ± 1.5 to 17.1 ± 1.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (P = 0.02), meanwhile the average $V_E$peak did tend to be higher (modest

	ventilation (VEpeak), VTpeak, peak breathing frequency (BFpeak), RERpeak, HRpeak and OUES were collected at baseline (once participants were able to perform more than 10 min of continuous FES rowing) and after 6 months of training, with a graded exercise test.	increase) (37.5 + 4.4 vs. 40.7 + 3.0 $L \cdot min^{-1}$, P = 0.09)*. 3. Both before and after training, injury level was directly related to $V_E$peak (R^2 = 0.48 and 0.43) and VO_2peak (R^2 = 0.70 and 0.55). Before training, the relationship of VO_2peak to $V_E$peak was strong (R^2 = 0.62), however, after training, this relationship became almost completely linearized (R^2 = 0.84). 4. For all 12 participants, the average OUES was higher after 6 months of FES-RT (1.24 ± 0.11 vs. 1.38 ± 0.12, P < 0.05). * Hence, improvements of cardiopulmonary reserve appear to be derived from cardiovascular and skeletal muscle adaptations and not from any improvement in ventilatory capacity.
Brurok et al. 2013 Norway Cross-over repeated measures Level 2 N = 15	**Population**: N=15 participants with AIS-A SCI Mean (SD) age: 39.0 (12.9) years Mean (SD) DOI: 13.2 (10.8) years **Treatment**: ACE: arm cycling FES_H: FES hybrid cycling (leg cycling + ACE) FES_{IH}: FES iso hybrid cycling (lower extremity pulsed isometric muscle contractions + ACE) **Outcome Measures:** Mean peak ventilation (V_E) and other physiological measures.	1. Significantly higher V_E during FES_{IH} (mean increase +8.21L/min) and during FES_H (+11.0L/min) compared to ACE in participants with SCI above T6. 2. No significant difference in V_E during FES_{IH} and during FES_H compared to ACE in participants with SCI below T6.
Jung et al. 2014 South Korea RCT PEDro = 5 Level 1b N = 20	**Population:** N=20 with SCI (12M, 8F) Mean (SD) age: 46.6 (10.5) years Mean (SD) DOI: 8.45 (3.56) years Injury level C8-L5, AIS-B to D. **Treatment:** Aqua group (10, aquatic exercise) Land group (10, control) Both groups performed upper extremity exercises; 1h sessions 3 times/week for 8 weeks. **Outcome Measures:** FVC, forced expiratory flow rate (FER), FEV_1, FEV_1-FVC ratio (FEV_1/FVC).	1. Significant between-group difference in change values of FVC (Aqua=1.8±1.3L, Land=0.31±1.6L; mean±SD) and FEV_1 (Aqua=1.1±1.2L, Land=0.21±0.3L). 2. Significant within-group increase in FVC (2.5±0.7 to 4.3±1.4L), FER (80.5±15.5 to 90.5±17.0L/s), FEV_1 (2.1±0.9 to 3.2±1.2L) and FEV_1/FVC (89.3±3.8 to 93.0±3.6%) in aqua group. 3. Significant within-group increase in FER (85.2±18.0 to 90.6±18.0L/s) in land group.

	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data.  	
[Tiftik et al. 2015](#) Turkey Prospective controlled trial Level 2 N = 52	**Population**: N=52 with SCI (40M, 12F) Mean (SD) age: 33.4 (13.9) years Mean (SD) DOI: 12.6 (13.0) months 18 AIS-A, 34 AIS-B/C/D 44 traumatic SCI, 8 non-traumatic SCI 17 cervical, 15 thoracic, 20 lumbosacral **Treatment:** Group A (26): locomotor training (using body weight supported treadmill training) + conventional rehab program; Group B (26): conventional rehab program only **Outcome Measures:** VC, FVC, FEV_1, FEV_1/FVC, forced expiratory flow rate 25-75% (FEV25-75), PEFR, MVV.	1. Significant increase in FVC (3.5±0.8 to 3.6±0.9L; mean±SD), FEV_1 (3.1±0.7 to 3.2±0.7L), FEV25-75 (3.8±1.0 to 4.0±1.1L) and VC (3.4±0.9 to 3.6±0.9L) in group A only. 2. Significant increase in FVC and VC in all group A subgroups after stratifying for injury completeness and severity. 3. Significant increase in MVV in both groups (Group A: 82.3±22.8 to 89.1±24.8L/min; Group B: 76.4±18.2 to 84.4±23.9L/min).
[Taylor et al. 2014](#) USA Pre-post Level4 N = 14	**Population:** N=14 people with SCI (13M 1F) Mean age (SD): 39.2(3.3) Mean DOI (SD): 9.7(2.6) years All AIS-A, level T3-T11 **Treatment**: 6 months of FESRT. **Outcome Measures:** $V_E$peak, peak aerobic capacity.	1. Significantly increased $V_E$peak after training. 2. Significant relation between level of injury and $V_E$peak before and after training.
[Terson de Paleville et al. 2013](#) USA Pre-post Level 4 N = 8	**Population:** 8 participants with complete (AIS-A) SCI and tetraplegia (7M, 1F). Mean (SD) age: 37 (18) years Mean (SD) DOI: 25 (12) months 5 cervical, 3 thoracic **Treatment:** Locomotor training with body weight support and treadmill. **Outcome Measures:** FVC, FEV_1, MIP, MEP, respiratory muscle sEMG and respiratory motor control assessment.	1. Significantly increased FVC, MIP, MEP, FEV_1 post compared to pre. 2. Significantly less baseline overall sEMG activity in SCI compared to NI* 3. Significantly increased overall sEMG activity post locomotor training for all tasks** 4. 7 participants had increased sEMG amplitudes for all tasks** after locomotor training 5. No significantly changes in distribution of sEMG activity post locomotor training for all tasks** 6. 1 participant developed activation in muscles post which were not activated pre

		7. Lower rate of muscle unit recruitment in patients with compered to NI* 8. Significantly faster muscle unit recruitment post compared to pre *Non-injured controls (NI), 9M 5F **Cough, inspiration/expiration tasks
Moreno et al. 2013 Brazil Pre-post Level 4 N = 15	**Population:** 15 male tetraplegic participants with SCI divided into control (n=7) and rugby players (n=8) groups. Control group: mean (SD) age: 33(9) yrs; DOI: 73(53) months. Rugby player group: mean (SD) age: 26(6) yrs; DOI: 87(52) months. **Treatment:** Experimental group participated in a regular 1-year wheelchair rugby training program that involved stretching, strength exercises, and cardiovascular resistance training (2-hour sessions 3-4x per week). **Outcome measures:** FVC, FEV_1, MVV.	1. There was a significant increase in all variables after training: mean (SD) FVC increased from 2.7 (0.9) L to 3.0 (1.0) L; FEV_1 increased from 2.5 (0.9) to 2.8 (1.0) L; MVV increased from 107 (28) to 114 (24) L/min. However, comparisons with the control group are not presented.
Lee et al. 2012 Korea Cohort Level 2 N = 38	**Population:** 38 patients with cervical SCI divided into experimental (MIE Feedback Resistive training) (n=19) and control groups (n=19). MI-EFRT group: 17M 2F; mean (SD) age: 45.7 (3.4) yrs; DOI: 20.0(1.5) months. Control group: 16M 3F; mean (SD) age: 50.1(3.6); DOI: 21.4(1.2) months. **Treatment:** Joint mobilization, stretching, and muscle strengthening for both groups 2x / day for 30 min, 5 x per week over 4-week period. A forced positive measure MI-E, along with expiratory muscle feedback respiration exercise was practiced by the experimental group, each for 15 mins. **Outcome measures:** Lung capacity, FVC, FEV_1, FEV_1/FVC	1. In the comparison of the values of respiratory function before and after the respiratory rehabilitation treatment, the experimental group showed a significant increase in VC(SD) from 42.3(4.9) to 47.0(4.7)%, FEV_1 from 1.3(1.1) to 1.5(0.1)L, and UPCF from 153.4(29.0) to 188.1(30.2) L/min. 2. Treatment had no significant effect on FEV_1/FVC. 3. In the comparison of changes in respiratory function after the respiratory rehabilitation treatment between the experimental and control group, there were significant differences between the changes in VC% (%), FEV_1 (L), and UPCF (L/min).
Jacobs 2009 USA Prospective controlled trial Level 2 N = 18	**Population:** 18 participants with SCI with complete motor paraplegia (level of injury T6-T10); participants were assigned either resistive training (RT) or endurance training (ET): RT group: 6M 3F; mean(SD) age: 33.8 (8.0) yrs ET group: 6M 3F; age: 29.0(9.9) yrs **Treatment:** Endurance training: 30 min of arm cranking exercise 3 times per week for 12 weeks; Resistance training: similar training but with training weights gradually increased every week.	1. Significant increase in VO_2peak in resistance training group (15.1%) and endurance training group (11.8%). 2. No significant change in $V_E$peak in either group.

	Outcome Measures: VO_2peak; $V_E$peak.	
Janssen & Pringle 2008 Netherlands Pre-post Level 4 N = 12	**Population:** 12 men with SCI (6 with tetraplegia and 6 paraplegia), including 4 participants (mean (SD) age: 44(14) yrs, DOI: 13(8) yrs) who had previous training on ES-LCE. **Treatment:** Computer controlled ES induced leg cycle ergometry (ES-LCE); total of 18 training sessions with each session lasting 25-30 min. **Outcome Measures:** VO_2, VCO_2, pulmonary ventilation (V_E).	1. Significantly higher peak values for VO_2 (+29%), VCO_2 (+22%), and V_E (+19%).
Valent et al. 2008 Netherlands Cohort Level 2 N = 137	**Population:** 137 participants with SCI; C5 or lower; aged 18-65 years. *Hand cycling group*: 35 participants with paraplegia, 20 with tetraplegia. *Non-hand cycling group*: 56 with paraplegia, 26 with tetraplegia. **Treatment:** All participants followed the usual care rehabilitation program in their own rehabilitation centres, with or without regular hand cycling exercise. Study included three measurements: 1) when participants could sit in a wheelchair for three hours; 2) on discharge; 3) 1 year after discharge. **Outcome Measures:** VO_2peak; FVC; PEFR.	1. Significant increase (26% in hand cycling group vs. 8% non-hand cycling group) in VO_2peak in paraplegic patients, whereas tetraplegic patients showed no change. 2. No change in pulmonary function (FVC or PEFR) found in either participants with paraplegia or tetraplegia.
Carvalho et al. 2006 Brazil Prospective controlled trial Level 2 N = 21	**Population:** (1) *Treatment group*: 11 males with complete tetraplegia, ages 22-50, C4-C7, 25-180 months post-injury (2) *Control group*: 10 males with complete tetraplegia, ages 23-42, C5-C8, 24-113 months post-injury **Treatment:** Treadmill training with neuro-muscular electrical stimulation (NMES): 20 min 30-50% BWS, 2x/wk. Conventional physiotherapy for control group. **Outcome Measures:** Metabolic and cardiorespiratory responses before and after training.	1. Significant differences were found in all parameters after treadmill training with NMES, except for HR and diastolic BP. During gait, VO_2 increased by 36%, VCO_2 increased by 43%, V_E increased by 30%, and systolic BP increased by 5%. 2. For the control group, only VO_2 and VCO_2 increased significantly at rest (31 and 16%, respectively) and during knee-extension exercises (26 and 17%, respectively).
Fukuoka et al. 2006 Japan Pre-post Level 4 N = 8	**Population:** N=8 (7M 1F); mean(SD) age: 46.5(8.3) yrs; AIS B; T7-L1. **Treatment:** *Wheelchair training program*: 30 min at 50% $HR_{reserve}$, 3x/wk, 60 day. **Outcome Measures:** VO_2 peak, HR.	1. Mean VO_2peak increased with training, became significant from 30th training day onwards (baseline = 17 ml/kg/min vs. T30 = 18 ml/kg/min). 2. Steady state HR decreased significantly by 15th training day, reached a plateau from day 15 onwards (baseline HR_{ss} = 123±11 bpm vs. at day 15 = 109±6 bpm).
Sutbeyaz et al. 2005 Turkey	**Population:** N=20 people with SCI (12 men, 8 women), 14 complete, 6 incomplete (T6-	1. After training, FVC, FEV_1, and VC, were significantly higher than the baseline values.

Pre-post Level 4 N = 20	T12), mean(SD) age: 31.3(8.2) yrs; DOI: 3.8(5.8) yrs. **Treatment:** Ventilatory and upper extremity muscle exercise: 1h, 3x/wk x 6 wks; Diaphragmatic, pursed lip breathing for 15min; Air shifting for 5min; voluntary IH 10min; arm-crank exercise. **Outcome measures**: Spirometry.	2. Exercise testing showed increased peak V_E and peak workload and a reduction in the ratio of physiological dead space to V_T compared to baseline values.
Le Foll-de-Moro et al. 2005 France Pre-post Level 4 N = 6	**Population:** N=6 participants (5M 1F), T6- & T11/12, mean (SD) age: 29 (14) yrs; mean DOI: 94 days. **Treatment**: Wheelchair Interval-training Program – 30 min (6 x 5 min bouts: 4 min moderate intensity and 1 min of high intensity) 3x/wk for 6 wks; Progressed throughout training program to achieve 50% and 80% of heart rate. **Outcome measures**: Spirometry.	1. At maximal exercise, peak V_E (75%), peak fb (-13.4%), peak V_T (+28.9%), and the ventilatory reserve (12.9%) improved after training. The oxygen cost of V_E decreased significantly (-20%) after training. 2. For the wheelchair test, at the same workload after training, V_E and fb decreased and V_T increased consistent with improved ventilatory efficiency and greater reliance on aerobic capacity after training. 3. Spirometric values and lung volumes showed small trends towards improvement after training.
Silva et al. 1998 Brazil Pre-post Level 4 N = 24	**Population:** 24 participants (12 people with paraplegia, 12 non-SCI participants), median age SCI: 31 yrs (range 22-54), control: 30 (range 22-52), T1-T12, all ASIA A, >3 yrs after injury. **Treatment:** Arm cranking aerobic training: 30 mins, 3x/wk x 6 wks. **Outcome measures**: Spirometry.	1. After aerobic training, SCI participants showed significant increases in FVC and the ventilatory muscle endurance, so that max voluntary ventilation at 70% time values post-training were not different from the initial values of non-SCI participants. 2. Severely limited ventilatory muscle endurance in people with paraplegia can be improved by arm cranking.
Hooker & Wells 1989 USA Pre-post Level 4 N = 8	**Population:** N=8 SCI (4M 4F); L*ow intensity group*: C5-T7 (age range 26-36yrs); *Moderate Intensity group*: C5-T9 (age range 23-36yrs) **Treatment:** Aerobic training: WC ergometry 20 min 3x/wk for 8 wk Low Intensity exercised at a power output = 50-60% of maximal heart rate. Moderate Intensity exercised at a power output = 70-80% maximal heart rate. **Outcome measures:** maximal oxygen uptake, peak power.	1. After training, no changes to maximal oxygen uptake or peak power. 2. No detectable changes during submaximal or maximal exercise were detected. 3. Training intensity was insufficient, participants did not comply with the program, or study was underpowered due to small sample size and heterogeneity of participant responses.

Discussion

Evidence for exercise training for the respiratory management in patients with SCI includes 6 RCTs, 6 prospective controlled trials and cohort studies, and 19 lower-level studies (mainly pre–post studies). Studies describing the acute responses to exercise in people with SCI were not included nor were studies that investigated competitive athletes with SCI. Included studies were difficult to interpret because of relatively small sample sizes, differences in exercise modality (wheelchair, arm crank exercise, body weight supported treadmill training, exoskeleton-assisted walking, functional electrical stimulation (FES) rowing, exergaming, pulmonary rehabilitation (strength training combined with respiratory training), passive leg cycling, or overground locomotion training) as well as inconsistent frequency, intensity and duration of exercise training. Nine studies included a control group (Silva et al. 1998; Carvalho et al. 2006; Lee et al. 2012; Moreno et al. 2013; Tiftik et al. 2015; Chen et al. 2016; Vivodtzed et al. 2020a; Vivodtzed et al. 2020b; Xiang et al. 2021), and the control groups in seven of the studies included participants comparable to those in the treatment group. This is in contrast to the control group used in Silva et al. 1998 study which consisted of non-SCI participants only; though healthy controls may be used for the normative values, they cannot be considered a true control group for people with SCI.

There is insufficient evidence to strongly support exercise training as a means to improve pulmonary function or ventilatory responses to exercise in people with SCI. However, some evidence (Le Foll-de-Moro et al. 2005; Qiu et al. 2016; Panza et al. 2019; Chen et al. 2016) indicated that following exercise training, VO2peak, aerobic efficiency (oxygen uptake efficiency slope [OUES]), FEV_1, FVC, maximal ventilation volume, FEV_1/FVC, peak V_E, V_T and ventilatory reserve improve. Two RCTs found significantly increased respiratory capacity testing exoskeleton (Xiang et al. 2021) walking or FES rowing (Vivodtzed et al. 2020b) with NIV when compared to sham training. Nevertheless, the training intensity needs to be relatively high (70-80% of maximum heart rate at a minimum of 3x/week for 6 weeks) as lower intensities did not show similar efficacy (Hooker & Wells 1989). Other studies showed no change in pulmonary function or ventilation during exercise (Valent et al. 2008; Jacobs 2009). Although 6 months of body-weight supported treadmill training in conjunction with neuromuscular electrical stimulation (NMES) was shown to be effective for improving peak measures of respiration, the intensity at which participants worked to achieve these outcomes is unclear, as each performed according to their individual capacity (Carvalho et al. 2006).

Conclusion

There is level 1 evidence (from one RCT: Xiang et al. 2021) that exoskeleton-assisted walking training for 4 weeks produces improvements at short-term in predicted FVC%, FEV_1, FEF_{75}, PEF, and MVV; and higher improvements in FVC, predicted FVC% and FEV_1 compared with conventional strength, aerobic, and balance training in patients with SCI.

There is level 2 evidence (from one RCT: Vivodtzed et al. 2020b) that whole-body hybrid FES-rowing training for 3 months with NIV provided better improvements in aerobic efficiency (OUES) (with an overall reduction in peak breathing frequency) and VO_2peak compared with the same training with sham NIV in patients with SCI.

There is level 4 evidence (from one pre-post study: Brizuela et al. 2020) that improvements in pulmonary parameters are higher in participants with lower cervical SCI than in participants with high cervical SCI after a stationary armcrank exercise for 8 weeks.

There is level 2 evidence (from two prospective controlled trials: Carvalho et al. 2006; Tiftik et al. 2015; and from one RCT: Chen et al. 2016) and level 4 evidence (from six pre-post studies: Silva et al. 1998; Sutbeyaz et al. 2005; Le Foll-de-Moro et al. 2005; Fukuoka et al. 2006; Terson de Paleville et al. 2013; Qiu et al. 2016) to support exercise training as an intervention that might improve resting and exercising respiratory function, and VO_2peak, and OUES in people with SCI.

There is level 4 evidence (from four pre – post studies: Panza et al. 2019; Panza & Guccione 2020; Panza et al. 2017; Gollie et al. 2017) that overground locomotor training (OLT) protocol provides some improvement in V_E, the phasic response to exercise (became faster), and walking endurance; and reductions in V_E variability, V_T variability, estimated work of breathing, VCO_2, $P_{ET}CO_2$, and in RPE in patients with SCI.

There is level 4 evidence (from one pre-post study: Janssen & Pringle 2008) that computer controlled electrical stimulation (ES) induced leg cycle ergometry (ES-LCE) increases the peak values of VO_2, CO_2, and pulmonary ventilation.

Key Points

For exercise training to improve respiratory function the training intensity must be relatively high (70-80% of maximum heart rate) performed three times per week for six weeks.

Ideal training regimens have not yet been identified.

10 Respiratory Muscle Training

As expected, the loss of inspiratory muscle function is related to the level of injury as illustrated in Figure 1. Dyspnea, defined as a subjective report of breathlessness or shortness of breath, is common in people with SCI and is greatest in people with tetraplegia (Ayas et al. 1999). Approximately two-thirds of the prevalence of dyspnea in this group is attributed to the inspiratory muscle loss (Spungen et al. 1997). Improved inspiratory muscle strength and endurance could potentially improve cough and maximal exercise ventilation in addition to decreasing dyspnea. The inspiratory muscles can be trained like the limb muscles with inexpensive devices that increase the resistive or threshold inspiratory load on the inspiratory muscles (Reid et al. 2010). Table 10 outlines common measures that are indicative of respiratory muscle strength and endurance. In neuromuscular disorders like SCI, maximal lung volumes that measure IC also can reflect increased inspiratory muscle strength.

Table 9. Measures of Respiratory Muscle Strength and Endurance

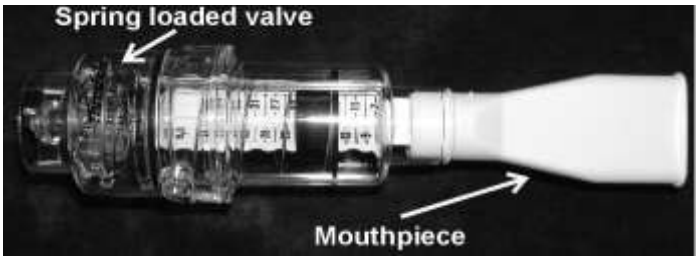
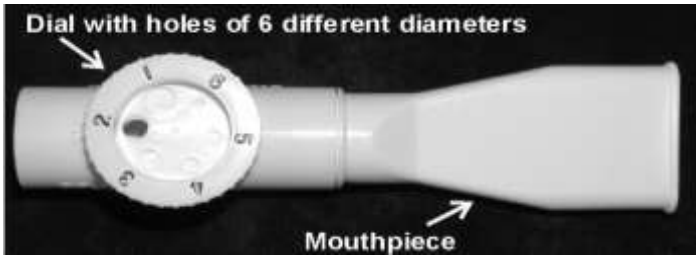
Term	Abbreviation	Definition
Maximal inspiratory pressure	MIP or PI_{max}	Estimate of inspiratory muscle force as reflected by the maximal pressure exerted by the inspiratory muscles measured at the mouth.
Maximal expiratory pressure	MEP or PE_{max}	Estimate of expiratory muscle force as reflected by the maximal pressure exerted by the expiratory muscles measured at the mouth.
Maximum voluntary ventilation	MVV	Maximum ventilation in 15 seconds, which reflects the "sprint" capacity of the respiratory muscles. The maximum ventilation can be measured over several minutes - between 4 and 15 min – which is more reflective of the endurance of the respiratory muscles.
Maximal sustainable mouth pressure	SIP	Maximum mouth pressure sustained during a 10-minute period of threshold loading, which is usually lower than the MIP. This is an estimate of the endurance of the inspiratory muscles.
Endurance time sustained on training load	T_{lim}	The endurance time while breathing on a resistive or threshold trainer at a defined level of the MIP
Maximal incremental threshold load	TL_{max}	The maximal load (usually defined as an inspiratory mouth pressure) attained on an incremental threshold loading test whereby the load is progressively increased every 2-3 min.

Evidence showing decreased dyspnea and improved strength and endurance after inspiratory muscle training (IMT) is well documented in healthy people (Karsten et al. 2018) people with other health conditions such as COPD (Reid et al. 2010; Geddes et al. 2005).

Figure 4. The Breather® Respiratory Muscle Trainer

Commercially available hand-held devices can be used for IMT. The four main types of devices are the resistive, threshold, isocapnic hyperpnea (IH), and incentive spirometers (Figure 5) (see Reid et al. 2010 for details of these training techniques).

- Threshold trainer: These devices, first used in patients with SCI by Ehrlich et al. 1999, have a one-way valve that closes during inspiration so that the person must breathe against a load; and the one-way valve opens during expiration such that no load is imposed during the expiratory phase of respiration.
- The resistive trainer imposes a load through a small diameter hole whereas the threshold trainer imposes a load via a spring-loaded valve. Regarding resistive trainers, also noteworthy for its widespread use, is the *POWERbreathe* device. However, as the authors of this module are aware, the only study using this model in participants with SCI showing the use of a hand-held electronic device (POWERbreathe KH1 device) was McDonald and Stiller (2019).
- IH imposes loading in a very different manner. The participant targets a prescribed ventilation level that requires higher inspiratory and expiratory flows. A bag attached to the device is adjusted to match the amount of rebreathing to maintain isocapnea i.e., a normal end-tidal CO_2 level.

	**Threshold trainer:** Has an adjustable spring-loaded valve that imposes the inspiratory load. The inspiratory load can be increased by winding the spring more tightly. Advantage of this trainer is that the same load is imposed on the inspiratory muscles regardless of breathing pattern. Threshold and P-Flex trainers available from Respironics HealthScan Inc., 41 Canfield Rd., Cedar Grove, NJ7, 0009-1201. 1-800-962-1266.
	**Resistive trainer:** Has holes of different diameters. The inspiratory load can be increased by setting the dial to holes of lesser diameter. Disadvantage of this trainer is that the participant can reduce the inspiratory load by breathing more slowly. If this device is used for training, a target must be used. Various targets have been designed that set a breathing rate (flow and/or inspiratory pressure) for the person.
	**Resistive trainer,** POWERbreathe "PLUS IMT" device: Consists of an IMT device comprising a mouthpiece, a main body, and a regulator which, by means of a valve, allows controlling the air passage resistance, thus allowing the inspiratory muscles to be trained (González-Montesinos et al. 2012). POWERbreathe "PLUS IMT" and POWERbreathe KH1 devices are available from POWERbreathe International Ltd., Northfield Road, Southam, Warwickshire, CV47 0FG, England, UK.
	**Resistive trainer,** *POWERbreathe KH1 device:* Hand-held electronic device which provides a variable flow resistive load via an electronically controlled valve, with loading maintained at the same relative intensity throughout the breath (Charususin et al. 2013). This enables practitioners to quantify the inspiratory load during IMT (Langer et al. 2013).

	**Isocapneic Hyperpnea Trainer:** Has a rebreathing bag that can be adjusted to ensure that the person's CO_2 level is maintained within a physiologic range. A target is provided for the person to increase the level of ventilation to a training intensity. This device enables training at low loads but much higher inspiratory and expiratory flow such that the inspiratory and expiratory muscles training at higher speeds of contraction. In contrast, the threshold and resistive trainers, place high loads while the speed of contraction is relatively low. SpiroTiger™ trainer available from FaCT Canada Consulting Ltd. 1215 Cariboo Hwy N Quesnel, BC V2J 2Y3 Canada1-877-322-8348
	**Incentive spirometry (Coach 2® device, MediMark):** An example of training was described by Shin et al. (2019), patients breathed through the mouthpiece slowly and as deeply as possible until the yellow piston indicator had reached the outlined area, to hold the breath for at least 5 s, and exhale slowly subsequently. Portex® Coach 2® Incentive Spirometer available from 3Z DENTAL SUPPLIES. 100 Leek Crescent, Suite 5, Richmond Hill, ON, Canada L4B 3E6.

Figure 5. Inspiratory Muscle Trainers

More recently, expiratory muscle training (EMT), has been added to IMT in patients with SCI as shown in some studies (Boswell-Ruys et al. 2020; Kader 2018; Kim et al. 2017b; Legg Ditterline et al. 2018; Gee et al. 2019) using complex devices (see examples of Expiratory Muscle Trainers in Figure 6).

	**PowerLung Trainer (PowerLung®):** Devices which have spring-loaded inspiratory and expiratory valves by which the pressure threshold could be adjusted as Gee et al. (2019) showed in their study. PowerLung® Trainer model available from PowerLung Inc. 1918 Triway Ln Houston, TX 77043 USA

	**Threshold PEP and IMT (Respironics):** Devices which compound threshold positive expiratory pressure and inspiratory muscle trainer which could be assembled together in order to provide resistance to the expiration and to inspiration as showed Aslan et al. 2016; Legg Ditterline et al. 2018; Kader 2018). Threshold PEP and IMT available from Philips Respironics. 1010 Murry Ridge Lane, Murrysville, PA 15668, USA

Figure 6. Expiratory Muscle Trainers

Respiratory training with bi-directional resistance will be considered RMT in this section (table 10).

Table 10. Inspiratory / Expiratory Muscle Training

Author Year Country Research Design Score Sample Size	Methods	Outcome
Boswell-Ruys et al. 2020 Australia RCT PEDro = 10 Level 1 N = 62	**Population:** 62 patients with tetraplegia (C4-C8) with related respiratory deficits; 58 males and 4 females; mean age 53,6 years; level of injury C4 (n = 21), C5 (n = 12), C6 (n = 16) and C7 (n = 13); AIS A (n = 32), AIS B (n = 9), and AIS C (n = 21). **Treatment:** Participants were allocated to sham (n = 32) or active (n = 30) treatment. All participants performed supervised RMT with a single threshold RMT device (the sham device was modified to hold the pressure valve permanently open). 3 to 5 sets of 12 breaths (IMT and EMT, separated by quiet breathing for 2 min) were performed twice daily, 5 days a week for 6 weeks, increasing 10% weekly of each participant's baseline PI_{max} and PE_{max} if tolerated. **Outcome Measures:** PI_{max}, (IC), VC, FVC, FEV_1, peak expiratory flow while coughing (PEFcough), TLC, PE_{max} at TLC, perceived breathlessness, respiratory-related morbidity,	1. After 6 weeks of RMT PI_{max} was significantly greater in the active group compared with the sham group; SGRQ score improved more in the active group compared with the sham group (mean between-group difference 10.3 points, 95% CI 0.01 to 20.65, p = 0.046); Borg scores for breathlessness during 10 inspiratory loaded breaths reduced more in the active group compared with the sham group (mean between-group difference 0.96, 95%CI 0.01 to 1.91, p = 0.049); and Borg scores at rest were greater in the sham group (mean between-group difference 0.64, 95% CI 0.11 to 1.17, p = 0.021). 2. After 1 year of unsupervised training, in comparison of baseline data, there was no significant difference between active and sham groups in any outcome measures except for the incidence of respiratory complications (there

	respiratory health (the St. George Respiratory Questionnaire [SGRQ]) and quality of live (the Short Form Health Survey: walk/ wheel (SF-36ww) and the EuroQol-Five Dimensional Visual Analogue Scale) were collected at baseline, 6 weeks and 1 year.	was a greater total number of respiratory complications in the sham group (n = 10) compared with the active group (n = 3), p = 0.017).
Soumyashree & Kaur 2020 India RCT PEDro = 7 Level 1 N = 27	**Population:** 27 participants with paraplegia; 22 males and 5 females; mean age 31.7 years; AIS A (n = 23) and AIS B (n = 4); level of injury T1-T12 (n = 7), T5-T7 (n = 6); and T8-T12 (n = 14); and mean time since injury 9.35 months. **Treatment:** Patients were divided in two groups, they performed 5 session a week during 4 weeks: ● IMT group (n = 15) trained used an Inspiratory Muscle Trainer with a resistance adjusted at 40% of the obtained MIP. The resistance was increased to the next level as the participants completed 50 breathes without difficulty for consecutive 3 days. Participants repeated this maneuver for 15 min with 2–3 min rest periods in between, 5 days per week for 4 weeks. ● Control group (n = 12) instructed to inspire maximally, predominantly with abdominal motion, while reducing upper ribcage motion. This cycle was repeated 60 times per session twice a day for 20 days. Intervention was given for 15 min. **Outcome Measures:** 12-minute wheel chair aerobic test (12-MWAT), multistage fitness test (MSFT), six minutes push test (6-MPT), MIP, MEP and Modified Borg dyspnea scale (MBS) were collected pre and post intervention.	1. Between group analysis showed that IMT group scored significantly better than control group on 12 MWAT (95% CI, 3.9 to 9.2), MSFT (95% CI, 1.0 to 3.3), 6-MPT (95% CI, 15.9 to 44.4), MIP (95% CI, −30.2 to −12.1), MEP (95% CI, 8.6 to 25.7) and on MBS score (95% CI, −3.2 to −0.6). 2. Within group analysis of IMT group showed significant improvements in MIP (P = 0.001) and MEP (P = 0.001), in MBS scores (P = 0.001), in VO_2max scores (P = 0.001) of 12 MWAT, in MSFT (P = 0.001), and in 6-MPT scores (P = 0.001) when compared with the baseline values. 3. Within group analysis of control group showed significant improvements on most of the outcomes variables after training.
Zhang et al. 2021 China RCT PEDro = 5 Level 2 N = 18	**Population:** 18 patients with SCI; 15 males and 3 females; mean age 32.5 years; mean time since injury 1.005 years; ASIA B (n = 13) and ASIA C (n = 5). **Treatment:** Patients were assigned to one of two groups. ● Music therapy group (n = 9) that performed oral motor respiratory	1. A significant increase was observed in the intervention group for FEV_1 from baseline to mid-term (t_1 = 0.83 ± 0.08 L, F = 18.61, P = 0.0001). 2. Compared with the control group, the IC (t_2 = 1.93 ± 0.57 L, F = 5.565, P = 0.0224), FEV_1 (t_2 = 0.92 ± 0.06 L, F = 9.988, P = 0.0027), FVC (t_2 = 2.32 ±

	exercise (OMREX) and vocal intonation therapy (VIT) (OMREX + VIT). ● Control group (n = 9) received routine respiratory function training. Therapy session of the two groups were both 30 min per day, 5 times a week, for a total of 12 consecutive weeks. **Outcome Measures:** Respiratory function tests (TLC, IC, residual capacity, FEV_1, FVC, maximal mid-expiratory flow rate (MMF), FEV_1/FVC, maximal inspiratory and expiratory flow volume loops), vocal assessment (sound pressure level (SPL) and voice quality), and questionnaires (SGRQ) and QoL) were collected at baseline (t_0), at 6 weeks (t_1) and after 12 weeks (t_2).	0.81 L, F = 8.813, P = 0.0047), and MMF (t_2 = 2.59 ± 0.27 L/s, F = 4.951, P = 0.0111) were increased, and the FEV_1/FVC (t_2 = 39.66 ± 8.51%, F = 15.96, P = 0.0002) was decreased in the intervention group at 12 weeks. 3. The SGRQ (t_2 = 50.91 ± 11.26, F = 6.345, P = 0.0170) and QoL (t_2 = 71.43 ± 13.53, F = 4.734, P = 0.0371) values in the intervention group were significantly lower (better) than those in control group at 12 weeks.
Kim et al. 2017b Korea RCT PEDro = 6 Level 1 N = 37	**Population:** 37 participants with SCI receiving inpatient treatment; 22 males and 15 females; mean age 40.5 years; time since injury 14.01 years; and level of injury C4-C5 (n = 6), C6-C7 (n = 7), T1-T2 (n = 6), T3-T4 (n = 10), and T5-T6 (n = 8). **Treatment:** Participants were divided in three groups: ● Control group, n = 12. ● RMT group, n = 12. ● Integrated training group (ITG) (RMT with additional abdominal drawing-in maneuver), n = 13. The participants received the RMT routine therapy for one hour, 3 times a week for 8 weeks. **Outcome Measures:** Spirometry (FVC and FEV_1) were collected before and after the intervention.	1. A comparison of the FVC and FEV1 prior to and following intervention showed a significant increase in the ITG and RMT group (P < 0.01). 2. Following intervention, FVC of the ITG and RMT group increased by an average of 19.98% and 10.41%, respectively, in comparison with the control group (increased by an average of only 1.78%) (p < 0.01). In addition, FEV_1 of the ITG and RMT group rose by an average of 16.71% and 9.80%, respectively, while that of the control group increased by an average of only 2.41% (p < 0.01). 3. Following the intervention, the FVC and FEV_1 of the ITG were increased further by an average of 9.75% and 7.01%, compared with those of the RMT group (p < 0.01).
Chen et al. 2016 China RCT PEDro = 4 Level 2 N = 98	**Population:** 98 males with traumatic SCI paraplegia; C5-C7; mean (SD) age 62.7 (± 10.8) years; mean (SD) time since injury 41.6 (± 10.8) years; and injury level T1-T2 (n = 39), T3-T4 (n = 32), and T5-T6 (n = 32). **Intervention:** Participants were divided in two groups:	1. The data analyses for 2 months, 4 months and 12 months displayed highly significant differences in pulmonary function and life-quality (P < 0.01) between experimental group and control group, the indicators of experimental group were higher than control group; but there was no difference (P >

	• Experimental group (n = 49) acquired pulmonary rehabilitation exercise for 12 months, consisting in breath training and strength training. Pulmonary rehabilitation exercises contained breath training (lip breathing and abdominal breathing, each training for 20 min and three times a day). • Control group (n = 49). All patients acquired conventional rehabilitation, including psychological rehabilitation and dietary guidance. **Outcome measures:** Pulmonary function (FEV_1, FVC, MVV) and FEV_1/FVC) and QOL (SF-36) were detected at baseline; during pulmonary rehabilitation at 2 months, 4 months, and 12 months; and after pulmonary rehabilitation 1 month.	0.05) after pulmonary rehabilitation 1 month between experimental group and control group.
Kader 2018 Egypt Prospective controlled trial Level 2 N = 36	**Population:** 32 patients with complete SCI, 23 males and 9 females, mean (SD) age 30.51 (± 6.82) years. **Treatment:** Patients were divided in two groups: • Group A (n = 16) performed RMT using an inspiratory muscle trainer with a threshold positive expiratory pressure device. The patient performed 6 work sets, 5 min in duration, with a rest period in between for 3 min. All patients performed a 45 min training/day, five days/week for six weeks. The training intensity was initiated with 20% of each participant PI_{max} and PE_{max} and progressively increased as tolerated up to 40% of PI_{max} and PE_{max} at the end of the training program. • Group B (n = 16): Control group. **Outcome Measures:** Arterial blood gases (PaO_2, $PaCO_2$ and pH), pulmonary function (FVC and FEV_1), heart rate (HR) and respiratory rate (RR).	1. The mean value of HR, RR, $PaCO_2$ and PH revealed significant reduction, where FVC, FEV_1 and PaO_2 revealed significant increase in group A at the end of the study. However, changes in group B were not significant. 2. There were significant differences between both groups at the end of the study in all the outcome measures (P < 0.05).
Raab et al. 2019 Switzerland Case control	**Population:** 67 patients with traumatic (n = 59) or non-traumatic (n = 8) SCI; motor lesion level from C4 to T12; 55	1. Effect size of 7% (95% confidence interval (CI) 2.8–11.6%) increase in PI_{max} per 10 units (cmH_2O) of

Level 3 N = 67	males and 12 females; mean age 50 (35 to 66) years; mean time post injury 1.9 (1.2-2.9) months; AIS A/B (n = 41) and AIS C/D (n = 26). **Treatment:** IMT with a training device for isolated inspiratory resistance with his valve calibrated and adjusted (9–41 cmH_2O) according to the participant's PI_{max}. IMT started about 6 weeks after injury and lasted for a period of about 6 consecutive weeks with 3–5 training sessions per week and with up to 90 repetitions per training session (according to the individual capacity, and individually and gradually increased). All participants received standard physiotherapy as part of the comprehensive in-patient rehabilitation program. **Outcome Measures:** Respiratory muscle strength (PI_{max} and PE_{max}), repetitions per session, number of training sessions, and training intensity (% resistance of the individual baseline value of PI_{max}).	increase in training intensity. The association of PI_{max} with training intensity was independent of AIS (test of interaction: $chi^2 = 0.18$, d.f. = 1, p = 0.67) and lesion level ($chi^2 = 0.00$, d.f. = 1, p = 0.99). 2. The effect of training intensity on PE_{max} was conditional on AIS (test of interaction: p < 0.021). While participants with motor complete lesions (AIS A/B) showed a 6.8% (95% CI 2.1 to 11.7%) increase in PE_{max} per 10 units (cmH_2O) of increase in training intensity, the corresponding adjusted effect size in the group with motor incomplete lesions (AIS C/D) was 0.1% (95% CI −4.3 to 4.5%).
Shin et al. 2019 Republic of Korea Case control Level 3 N = 104	**Population:** 104 patients with acute (n = 14), subacute (n = 42), and chronic (n = 48) SCI; 78 males and 26 females; mean (SD) age 48.7 (± 17.5) years; AIS A (n = 21), AIS B (n = 7), AIS C (n = 30) and AIS D (n = 46); injury severity (complete, n = 21 and incomplete, n = 83); level of injury (tetraplegia, n = 65, paraplegia, n = 39); and mean (SD) disease duration 97.4 (± 139.2) days. **Treatment:** Self-directed RMT and care for 4 weeks (more than 5 days a week) consisting in GPB exercises, IMT using incentive spirometry, and air stacking exercises with a resuscitation bag. Patients were subgrouped by injury severity, level of injury and disease duration for analysis. **Outcome Measures:** Pulmonary function evaluation (FVC in sitting position (ΔFVCsit), FVC in supine (ΔFVCsup), and PCF (ΔPCF)) before and after the short-term rehabilitation therapy.	1. FVCsup, FVCsit, and PCF were more severely affected in the tetraplegic group compared to the paraplegic group (P < 0.01) at baseline. 2. The absolute value of FVCsup was significantly higher compared with that of FVCsit at the initial and final assessment in all subgroups, except for the acute group. 3. After treatment protocol, the absolute values of FVCsup, FVCsit, and PCF had significantly improved in all subgroups regardless of the injury level and severity, as well as disease duration. 4. The subacute group showed the highest improvement in ΔFVCsit and ΔPCF, compared with the acute and chronic groups (P < 0.05); and a greater ΔFVCsup compared with the chronic group (P = 0.002) and a higher tendency compared with the acute group (P = 0.056).

Gee et al. 2019 Canada Pre – Post Level 4 N = 6	**Population:** 6 wheelchair rugby athletes with SCI; 5 males and one female; age 33 ± 5 years; time since injury 157 ± 63 months. **Treatment:** Participants performed RMT consisting in two series of 30 repetitions, on 5 days of the week for 6 weeks. Initial inspiratory and expiratory pressure thresholds were set at 60% MIP and MEP determined at baseline. Resistance was increased once the participant could comfortably complete all 30 breaths and the associated dyspnea for each session that week was less than 6/10 on the Modified Borg Dyspnea Scale. **Outcome Measures:** Resting pulmonary function (MIP, MEP, IC, VC, expiratory and inspiratory reserve volume, FVC, FEV_1, PEF, TLC, and RV); resting cardiac function (left-ventricular end-diastolic volume, left ventricular end-systolic volume, left-ventricular stroke volume, ejection fraction, early and late diastolic filling velocities, ratio of early to late diastolic filling, mitral annular velocities during systole, early and late diastole, and BP [blood pressure]); exercise capacity (during maximal and submaximal tests); exercising lung volumes; field-based exercise performance (20 × 20 m repeated sprint field test); and adherence, dyspnea and intensity during the exercise sessions were assessed at pre-RMT, post-RMT and after a 6-week no RMT period.	1. Pulmonary function: a. From pre- to post- RMT both MIP (40%, p = 0.002) and MEP (25%, p = 0.007) increased without an increase from pre- to follow up assessment. b. PEF increased by 9% from pre- to post-RMT and remained elevated at follow-up (6.74 ± 1.51 *vs.* 7.32 ± 1.60 *vs.* 7.29 ± 1.85 L s^{-1}, both $P < 0.04$ vs. pre-RMT). c. Resting lung volumes and capacities were unchanged from pre-RMT at post-RMT and follow-up, except that FRC was significantly lower at follow-up compared to pre-RMT (3.70 ± 1.29 *vs.* 3.23 ± 0.99 l, $P = 0.021$). 2. Exercise capacity: a. Peak work rate was higher post-RMT (68 ± 22 W) than both pre-RMT (60 ± 23 W, P = 0.003) and at follow-up (63 ± 23 W, $P = 0.037$). b. VO_2peak increased in all athletes after RMT (1.24 ± 0.40 *vs.* 1.40 ± 0.50 l min^{-1}, $P = 0.12$) and was significantly lower at follow-up compared to post-RMT (1.40 ± 0.50 *vs.* 1.18 ± 45 l min^{-1}, $P = 0.041$). c. There were non-significant differences in peak V_E, average expiratory flow rate, oxygen pulse, work rate at the first or second ventilatory threshold, peak RER, V_T, fb, or peak HR between any time-points.
Leathem et al. 2021 USA Case series Level 4 N = 6	**Population:** 6 participants with SCI; 5 males and 1 female; incomplete injury (n = 4) and complete injury (n = 2); cervical injury (n = 4) and thoracic injury (n = 2); mean (SD) age 33 (± 18.6) years; and mean (SD) time since injury 7 (± 4) years. **Treatment:** Treatment consisted in two modalities over 8 weeks: ● Spinal Mobility X class: Each four-hour class (once per week) was comprised of three circuits:	1. None of the participants reported adverse effects due to the respiratory training; and they reported various improvements in the surveys. 2. Mean difference for all measures across participants indicates overall improvement in all four functional outcome measures.

	strengthening, aerobic training, and spinal mobility. ● IMT at home: Participants were trained in the use of a IMT device which provides consistent pressure for inspiratory muscle strength and endurance training, regardless of speed of breath. The training goal was to achieve 30 breaths, over 2 sessions a day, 5 days a week, over the training period, while resistance was progressed weekly. **Outcome Measures:** Subjective survey, transfer test, t-shirt test, four directional reach test, and four-directional trunk test were collected before and after the program.	
Legg Ditterline et al. 2018 USA Pre – post Level 4 N = 44	**Population:** 44 participants with chronic SCI; 35 males and 9 females; mean age 39.5 years; level of injury C2 (n = 3), C3 (n = 4), C4 (n = 13), C6 (n = 3), T1 (n = 1), T2 (n = 3), T4 (n = 3), T6 (n = 4), T9 (n = 2), and T11 (n = 3); AIS A (n = 17), AIS B (n = 10), AIS C (n = 12) and AIS D (n = 5); and mean time since injury 102 months. **Treatment:** Participants were divided in: ● RMT Group (n = 24): Consisted in 20 sessions (for 4 weeks) of 45-minute training using a threshold positive expiratory pressure device and inspiratory muscle trainer assembled together using a 3-way valve system. Training load was increased regularly so participants were training at 60% of their PI_{max} and PE_{max} by the last week. ● Control group (n = 20). **Outcome Measures:** FVC, FEV_1, and beat-to-beat arterial blood pressure, heart rate changes during the 5-second-long maximum expiratory pressure maneuver (5s MEP) and the sit-up orthostatic stress test were collected before and after the intervention program.	1. Pulmonary function outcomes increased significantly in the RMT group compared with controls (FVC increased from 76% ± 13% to 82% ± 13% ($P < 0.01$), and FEV_1 increased from 68% ± 15% to 76% ± 15% ($P < 0.01$)). 2. Baroreflex sensitivity increases significantly in the trained group in response to maximal, acute expiratory effort that were not seen in the control group.

Shanmuga Priva & Kalpana 2018 India Pre – post Level 4 N = 20	**Population:** 20 males with chronic traumatic SCI (C5-T12). **Treatment:** Participants were divided in two groups: ● Group I, n = 10, received convectional chest physiotherapy including diaphragmatic breathing exercise, air shift maneuver, assisted coughing and active cycle of breathing technique. ● Group II, n = 10, received both IMT and the conventional chest physiotherapy. IMT was performed 2 sessions of 15 min per day, 4 days per week, for a period of 8 weeks; load was set at 30% of PI_{max}. **Outcome Measures:** RPE, PI_{max}, PE_{max}, and PEFR.	1. There was a statistically significant improvement in Group II vs. group I in PI_{max}, PE_{max} and PEFR.
Zhang et al. 2016 USA Pre – post Level 4 N = 6	**Population:** 6 males with cervical (C4-C7) SCI; mean (SD) age 48 (± 7.1) years; mean (SD) time since injury 16 (± 8.5) years; AIS A (n = 4) and AIS B (n = 2); level of injury C4 (n = 1), C5 (n = 2), C6 (n = 2) and C6-C7 (n = 1). **Treatment:** Participants underwent 10 min of functional magnetic stimulation (FMS) conditioning of the inspiratory muscles and 10 min FMS conditioning of the expiratory muscles (with 10-min break between); twice per day; 5 days per week, for 6 weeks. **Outcome Measures:** PI_{max} at RV, PE_{max} at TLC, IRV, ERV, PIF at RV, PEF at TLC, and compound muscle action potential of first and ninth lower intercostal muscles were collected before, during, and after the FMS protocol, and at a 4-week postconditioning period.	1. The CMAP amplitudes increased only as the magnetic stimulation intensity increased from 40% to 80% of maximal intensity of the magnetic stimulator. 2. No medical complications, pain or adverse effects were noted during the study period, except for one patient who reported paresthesias in his right upper arm (with a history of paresthesias). 3. Continuous improvements in inspiratory and expiratory functions were observed after 2, 4 and 6 weeks of conditioning, compared from baseline. 4. 4 weeks after conditioning MIP, IRV, PIF, MEP, ERV, and PEF decreased a 4.3%, 6%, 5.4%, 1.0%, 4.0%, and 8.1% respectively, from their values at the end of the 6-week conditioning protocol. Still, there were significant improvements in MIP ($p = 0.040$), PIF ($p = 0.0057$), MEP (0.035), PEF (0.003), and ERV ($p = 0.035$)), when compared with the baseline.
Postma et al. 2014; Netherlands	**Population:** 40 participants with SCI (35M, 5F) Mean (SD) age: 46.8 (14.3) years	1. Significantly greater increase in MIP in resistive IMT group (56.4±29.5 to 82.7±29.7cmH2O; mean±SD) than control group

<table>
<tr>
<td rowspan="2">RCT
PEDro = 7
Level 1
N = 40</td>
<td>Median (IQR) DOI: 74 (57-109) days for resistive IMT group & 88 (59-121) days for control group
30 tetraplegia, 10 paraplegia
24 motor complete SCI.
Treatment: Resistive IMT group (19): 8 weeks using IMT trainer + usual care; Control group (21): Usual care.
Outcome Measures: FVC, FEV_1, PEFR MVV, MIP, MEP, visual analogue scale for subjective breathing, and Short-Form-36.</td>
<td>(56.1±23.5 to 70.7±28.1cmH2O) 1 week after intervention period, but loss of significance at 8 weeks and 1 year follow-ups.
2. MIP improved over longer period for those who continued resistive IMT post-intervention, compared to those who discontinued.
3. No significant between-group difference in changes of any other pulmonary outcome measure.</td>
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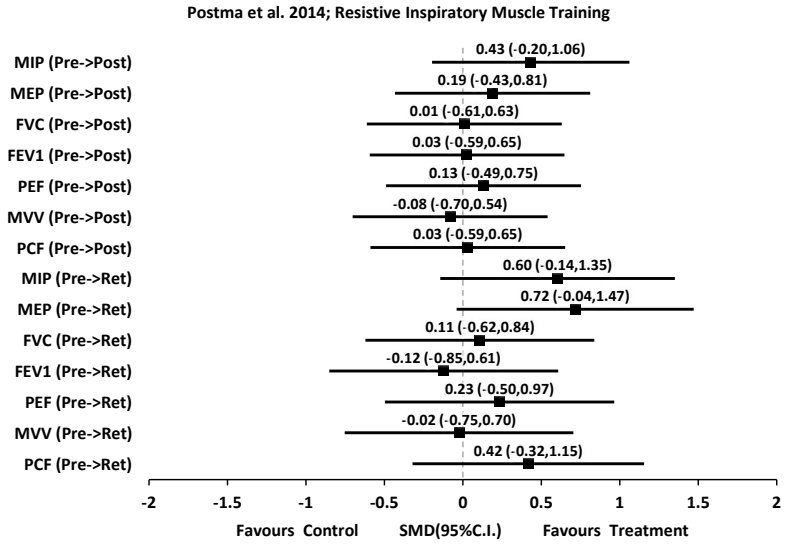
<td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data
 
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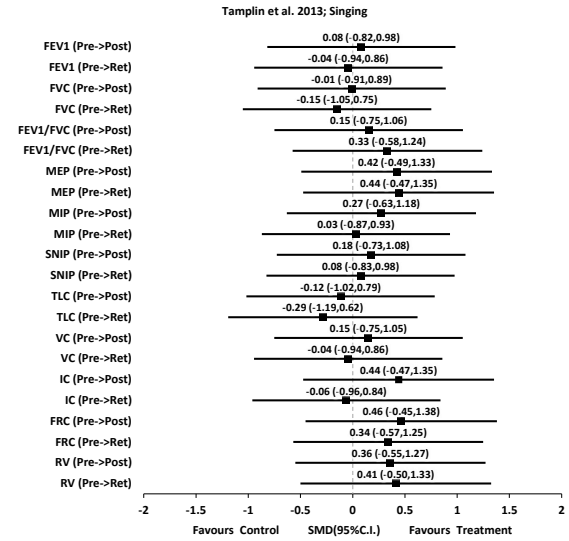
<tr>
<td>West et al. 2014
UK
RCT
PEDro = 4
Level 2
N = 10</td>
<td>Population: 10 athletes with cervical SCI (9M, 1F)
Mean (SD) age: 29.2 (2.7) years
Mean (SD) DOI: 9 (2.2) years
7 AIS-A, 3 AIS-B.
Treatment: IMT group (5): 6-week IMT; Placebo group (5).
Outcome Measures: Diaphragm thickness, MIP, MEP, FEV_1, PIF rate, PEFR, MVV and other cardiovascular and physiological measures.</td>
<td>1. Increase in diaphragm thickness (+22% IMT vs. -3% placebo) and MIP (+11% vs. -6%) is significant between-groups
2. Significant increase in MVV for both groups; increase insignificant between-groups
3. No evidence of activity-related dyspnea in either group pre- or post-intervention
4. No correlation between percentage change in diaphragm thickness and maximum static inspiratory pressure.</td>
</tr>
</table>

Fischer et al. 2014 Italy Case control Level 4 N = 12	**Population:** 12 hand bike athletes with SCI (10M, 2F) Mean (SD) age: 43 (5.4) years Median (SD) DOI: 16.4 (7.3) years All lesions between T2-T12. **Treatment:** Control (5): no intervention; Experimental (7): 20 sessions of respiratory muscle endurance training. **Outcome Measures:** VC, FVC, TV, maximal TV, FEV_1, FEV_1/FVC, PEFR, MVV, maximal V_E ($V_E$max), maximal fb (fRmax), respiratory endurance time and other physiological measures.	1. No significant between group changes in all resting lung function measurements. 2. Significant within-group increase in fRmax, VEmax & respiratory endurance time after respiratory muscle endurance training only.
Aslan et al. 2016 USA Case control Level 3 N = 11	**Population:** 11 participants with SCI (8M, 3F) Mean (SD) age: 32(9) years Median (SD) DOI: 53(72) months 10 cervical, 1 thoracic AIS-A/B/C: 3/4/4 **Treatment:** 1 month of RMT. **Outcome Measures:** FVC, FEV_1, MIP, MEP, respiratory rate, and other physiological measures.	1. Significantly increased FVC after RMT. 2. No significant changes in other pulmonary measures.
Tamplin et al. 2013 Australia RCT PEDro = 8 Level 1 N = 24	**Population:** 24 participants with chronic tetraplegia (C4-C8, AIS A & B) were randomized to the experimental group (n=13) or control group (n=11). *Intervention group*: mean (SD) age: 44 (15) yrs; DOI: 13(7) yrs. *Control group*: mean (SD) age: 47(13) yrs; DOI: 8(6) yrs. **Treatment:** The experimental group received group singing training 3 times weekly for 12 weeks. The control group received group music appreciation and relaxation for 12 weeks. Assessments were conducted pre, mid-, immediately post-, and 6-months postintervention. **Outcome measures:** Standard respiratory function testing, sEMG from accessory respiratory muscles; sound pressure levels during vocal tasks, assessments of voice quality, voice handicap index, profile of mood states, and assessment of QOL.	1. The singing group increased projected speech intensity and maximum phonation length significantly more than the control group. 2. Both groups demonstrated an improvement in mood, which was maintained in the music appreciation and relaxation group after 6 months. 3. No change in respiratory muscle strength was shown.

<table>
<tr><td></td><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data.
 
</td></tr>
<tr><td>Van Houtte et al. 2008
Belgium
RCT
PEDro = 8
Level 1
N = 14</td><td>Population: C4-T11 AIS A,B, or C; 2-6 months since injury.
Treatment: sham or normocapnic hyperpnea training for 15-30 min x 8 wks; average of 27 sham and 28 training sessions.
Outcome measures: MIP, VC, MVV, respiratory muscle endurance, RI.</td><td>1. Significant increase in MIP, VC, MVV, and respiratory muscle endurance and lung volumes after IMT.
2. Number of RI was less in the training than the sham group (1 vs. 14).</td></tr>
<tr><td rowspan="2">Mueller et al. 2012 & 2013
Switzerland
RCT
PEDro = 5
Level 2
N = 24</td><td>Population: 24 participants with traumatic complete tetraplegia (C5-C8, AIS A) were randomly assigned to 1 of 3 groups. Placebo group: 6M 2F; mean (SD) age: 41.6(17.0) yrs; DOI: 6.6(1.4) months. Isocapnic hyperpnea (IH) group: 6M 2F; mean (SD) age: 33.5(11.7) yrs; DOI: 6.6(0.9) months. Inspiratory resistive training (IRT) group: 6M 2F; mean (SD) age: 35.2(12.7) yrs; DOI: 6.0(0.0) months.
Treatment: All participants completed 32 supervised training sessions over 8 weeks.
Outcome measures: Inspiratory and expiratory muscle strength.</td><td>1. Compared to placebo training, IRT showed high effect sizes for inspiratory muscle strength (d=1.19), VAS values of “cleaning the nose” (d=0.99), and the physical component of subjective QOL (d=0.84).
2. IH compared with placebo showed a high effect size for breathlessness during exercise (d=0.81).
3. Friedman analysis showed a significant effect for IRT vs. placebo and vs. IH on inspiratory muscle strength.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention (IH and IRT respectively) data.</td></tr>
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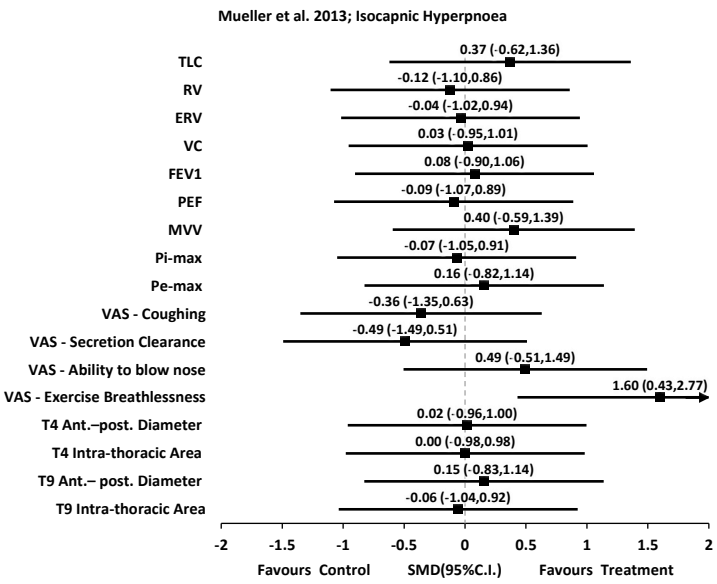
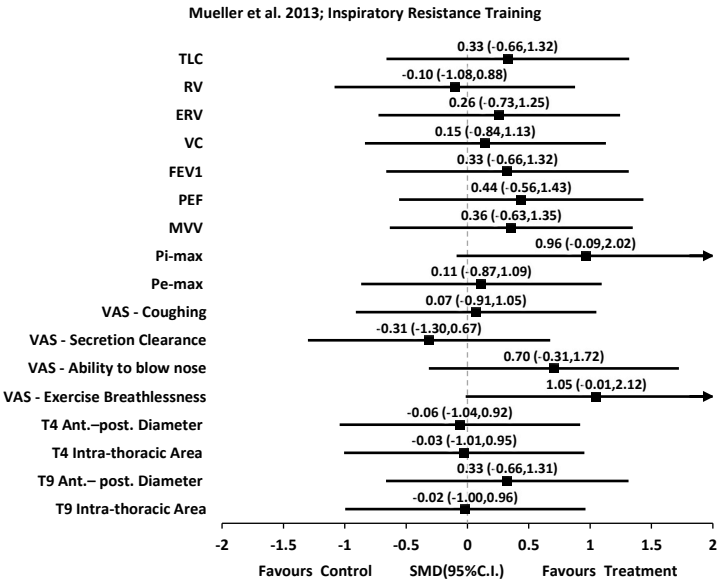
<td colspan="2"> 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<tr>
<td>Loveridge et al. 1989
Canada
RCT
PEDro = 5
Level 2
N = 12</td>
<td>Population: 12 participants with complete motor loss below C6-C7 (n=6 control, n=6 training) >1yr post injury, mean(SD) age IMT:31(4.1) yrs, Controls: 35(12) yrs.
Treatment: Resistive IMT without target at 85% maximal sustainable mouth pressure (SIP) for 15 min twice daily, 5 days per wk × 8 wks.
Outcome measures: Spirometry.</td>
<td>1. Increase in MIP and SIP in both the control group (30%±19% and 31%±18% respectively), and IMT group (42% ± 24% and 78% ± 49% respectively) but no difference in post-training improvements between groups.
2. The increased MIP and SIP resulted in a slower and deeper breathing pattern and a significantly shorter inspiratory time: total time of respiratory cycle in both trainers and control participants.</td>
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Litchke et al. 2012 USA Pre-post Level 4 N = 24 (22 SCI)	**Population:** 24 males (22 with tetraplegia, 1 with spastic cerebral palsy, and 1 with congenital upper and lower limb deformities) randomly assigned to 1 of 3 groups: 1) inspiratory and expiratory resistive training (n=8); 2) inspiratory and expiratory threshold training (n=8); 3) controls (n=8). Age range: 17-35 yrs; DOI range: 6 months to 17 years. **Treatment:** Resistive group trained with the Expand-a-Lung;1 set of 10 breathing cycles 3x per day for 9 weeks. Threshold group trained with the PowerLung Performer model; 3 sets of 10 breathing cycles 3 times per day every day for 9 weeks. **Outcome measures:** SF-36v2	1. 16 participants completed the study (Threshold=4, Resistive=5, CON=7). 2. Resistive RMT showed reductions in bodily pain and improvements in vitality domains of the SF36 vs. CON values. The mechanism of decreased pain because of RMT is difficult to determine. However, due to the significance of pain on HRQOL, this outcome is worthy of further consideration.
Uijl et al. 1999 Netherlands Prospective controlled trial Level 2 N = 10	**Population:** 10 participants recruited; 9 participants completed (8M 1F), all with tetraplegia C3-C7, 2-27yrs post-injury; AIS A (n=3), B (n=3), C and D (n=3); Age: mean 34.4 yrs (range 20-49 yrs). **Treatment:** No resistive sham training (6 weeks) then Target flow IMT (6 weeks). 15 min twice daily for each phase of 6 wks. **Outcome measures:** Spirometry, MIP, Maximal incremental threshold load (TL_{max}).	1. TL_{max}, a measure of inspiratory muscle endurance increased after both sham training and IMT. 2. No significant improvement in MIP for either group or differences in post-training change between groups. 3. Significant increase in peak power, V_T and VO_2 during maximal exercise test at 6-12wks of IMT.
Rutchik et al. 1998 USA Pre-post Level 2 N = 9	**Population:** 9 people with SCI; C4-C7; >1 yr since injury; Age: 24-65 yrs with mean 36 yrs **Treatment:** Resistive IMT without target 15 min twice daily × 8 wks. **Outcome measures**: MIP, spirometry.	1. Significant increase in MIP and lung volumes after IMT. 2. At 6 months, 4 months after training stopped, trends towards baseline and repeat measures in 7 of 8 participants showed no difference between baseline and 6 months outcomes. 3. Compliance ranged between 48 and 100% of IMT sessions.
Hornstein & Ledsome 1986 Canada Case series Level 4 N = 20	**Population:** 20 participants (18M 2F) in acute post-traumatic phase; 10 tested at 4 months, 10 others were discharged, non-compliant or had medical complications. **Treatment:** Resistive IMT without target 15min 2x/day ×6wks. **Outcome measures**: MIP.	1. Four months after IMT began, 10 participants showed improvement in MIP from mean (SD) 45(4.1) mmHg to 59(6.8) mm Hg but no statistics were performed on data. 2. Two case reports showed improvement in MIP and decreased dyspnea.

Discussion

Two meta-analyses (Tamplin & Berlowitz 2014, N = 212; Wang et al. 2020, N = 448) demonstrated RMT improved pulmonary strength and respiratory parameters in people with SCI. Participants showed a range of improvements in VC, MIP, MEP, and MVV. Similarly, Lemos et al. (2020) found improvements in pulmonary function and respiratory muscle strength/endurance, but showed no effect on improving cardiorespiratory fitness (i.e., VO_2max). Due to major variability across studies, they also could not establish which RMT type and protocol should be used to maximize benefits in athletes and non-athletes with SCI.

Studies have suggested that inspiratory resistive training (Mueller et al. 2012 and 2013; Soumyashree & Kaur 2020; Postma et al. 2014; Raab et al. 2019; West et al. 2014), respiratory muscular training (Boswell-Ruys et al. 2020), and normocapneic hyperpnea training (Van Houtte et al. 2008) significantly increases inspiratory muscle strength. Raab et al. 2019 and Soumyashree & Kaur 2020) found that IMT could increase expiratory muscle strength. Other researchers found similar success in improving pulmonary function (as measured by FVC, FEV_1, PEF, PEFR, MVV and/or FEV_1/FEV ratio) using IMT, RMT alone and when pairing RMT with an additional abdominal drawing-in maneuver (Aslan et al. 2016; Kader 2018; Shin et al. 2019; Kim et al. 2017b; West et al. 2014). Two RCTs provide level 1a evidence that RMT (Boswell-Ruys et al. 2020) and IMT (Soumyashree & Kaur 2020) improve functionality and exercise capacity as measured by 12 minute wheel chair aerobic test (12-MWAT), multistage fitness test (MSFT), and the six minutes push test (6-MPT).

Some studies combined various breathing techniques as part of a complex rehabilitation protocol. Chen et al. (2016) showed that patients receiving pulmonary rehabilitation, including breath training (lip breathing and abdominal breathing) and strength training (upper limb training such as arm crank cycle training) improved pulmonary function and life-quality during the 12 months of training in participants with SCI, compared to patients of the control group. Meanwhile, Shin et al. (2019) showed improvement in the absolute values of FVC, and PCF in patients who received RMT and care consisting of glossopharyngeal breathing (GPB) exercise, IMT using incentive spirometry, and air stacking exercises with a resuscitation bag for 4 weeks. The RCT published by Tamplin et al. (2013) showed that group singing exercises significantly improve phonation, and projected speech intensity; and Zhang et al. (2021) indicated that oral motor RMT and vocal intonation therapy improve IC, FEV_1, maximal mid-expiratory flow rate, FEV_1/FVC and SGRQ.

In addition, some studies have shown that RMT has the potential to dramatically reduce respiratory infections (RI) (Boswell-Ruys et al. 2020; Van Houtte et al. 2008).

Regarding parameters of training, great variability in dosage, repetitions, series, weekly frequency, and duration of training exists. Majority of studies reported that intensity of inspiratory and/or expiratory training was set at baseline with a range between 20% to 60% of MEP and MIP (Boswell-Ruys et al. 2020, Gee et al. 2019; Legg Ditterline et al. 2018; Postma et al. 2014; Raab et al. 2019; Soumyashree & Kaur 2020; Kader 2018; West et al. 2014). Studies described a progressive increase of the load (usually a 10% increase weekly or when RPE stabilizes or decreases) with a maximum load of 70 – 90% MIP and/or MEP at baseline; while

one study reported that load increased weekly regarding MIP and MEP values were assessed weekly (60% MIP or MEP of last week) (Legg Ditterline et al. 2018).

Some previous studies could not be included in meta-analyses because of differences in training techniques or protocol, heterogeneity of participant characteristics, and/or differing measurement of outcomes. brooks

Future research to more accurately determine a treatment effect of IMT, EMT, and RMT after SCI should use: 1) larger samples; 2) outcome measures of inspiratory - expiratory muscle strength and endurance, dyspnea, QOL, and daily function; 3) optimal training techniques of threshold loading, targeted resistive devices, or normocapnic hyperpnea; 4) a comparison of the effectiveness of IMT, EMT, or RMT relative to or as an adjunct to other rehabilitation interventions. Of equal importance, overly aggressive prescriptions of IMT can fatigue and injure the inspiratory muscles, increasing the person's predisposition to respiratory compromise. Reid et al. (2010) outlines parameters to monitor during IMT in order to avoid untoward responses such as muscle fatigue and hypercapnia. Parameters include: intensity of load, mode of load, duration, frequency and length of training to ensure adequate training protocol; blood pressure, heart rate, respiratory rate, other signs and symptoms of respiratory distress or inability to tolerate exercise load as signs of exercise intolerance; discoordinate chest wall movement, excessive dyspnea during training, long lasting complaints of fatigue after training sessions to avoid inspiratory muscle fatigue; signs of delayed-onset muscle soreness, reduced strength and endurance to avoid muscle injury; and end-tidal CO_2, SpO_2 and signs of headache, confusion to avoid hypercapnea (Reid et al. 2010). Van Houtte et al. (2008) provided 48 hours rest after their participants were unable to tolerate an overly intense workload.

For IMT to improve ventilation, decrease dyspnea, and to improve daily function after SCI, parameters to optimize IMT are currently only available for people with other respiratory conditions. For people with COPD, the optimal IMT protocol should use threshold or targeted resistive trainers:

- At an intensity of 30-70% of MIP,
- For a duration up to 30 min per session, performed continuously or in intervals, 4-6 days/week and be continued indefinitely (Geddes et al. 2006).
- Progression of intensity (MIP) should not exceed 5% per week.

Conclusion

There is level 1 evidence (from two RCTs: Boswell-Ruys et al. 2020; Kim et al. 2017b), level 2 evidence (from one prospective controlled trial: Kader 2018), level 3 evidence (from one case-control study: Aslan et al. 2016) and level 4 evidence (from two pre – post studies: Legg Ditterline et al. 2018; Gee et al. 2019) that RMT (IMT + EMT) as an intervention will improve inspiratory and expiratory muscle strength, pulmonary function and functionality and exercise capacity in people with SCI.

There is level 1 evidence (from three RCTs: Soumyashree & Kaur 2020; Van Houtte et al. 2008; Postma et al. 2014), level 2 evidence (from three RCTs: Mueller et al. 2012/2013; Loveridge et al. 1989; West et al. 2014), level 3 evidence (from one retrospective study: Raab et al. 2019), and

level 4 evidence (from several pre-post and case studies) to support IMT as an intervention that will improve inspiratory and expiratory muscle strength, pulmonary function, functionality and might decrease dyspnea and RI in people with SCI.

There is level 1 evidence (from one RCT: Kim et al. 2017b) that the performance of RMT combined with the abdominal drawing-in maneuver improves more in FVC and FEV_1 than RMT alone in patients with chronic SCI.

There is level 1 evidence (from two RCTs: Tamplin et al. 2013; Zhang et al. 2021) that music and vocal intonation rehabilitation (e.g., group singing exercises, oral motor RMT, and vocal intonation therapy) improves phonation, projected speech intensity, IC, FEV_1, maximal mid-expiratory flow rate, FEV_1/FVC, and SGRQ in patients with SCI.

There is level 2 evidence (from one RCT: Chen et al. 2016), level 3 evidence (from one case control study: Shin et al. 2019), and level 4 evidence (from two pre – post studies: Leathem et al. 2021; Shanmuga Priya & Kalpana 2018) that different combinations of breathing training exercises, and general body exercises, improve pulmonary function, functionality and QOL in patients with SCI.

There is level 4 evidence (from one pre – post study: Zhang et al. 2016) that functional magnetic stimulation (FMS) conditioning is safe and effective to improve the inspiratory and expiratory function of patients with SCI.

Key Points

Respiratory muscle training (including IMT, IMT + EMT, and different combinations of other breathing training exercises) generally improves respiratory muscle strength and endurance, pulmonary function, and functionality in people with SCI.

Dosage of RMT should be defined as there is lack of defined protocol among research in SCI.

10.1 Intermittent Hypoxia

Intermittent hypoxia is usually studied as a complication contributing to other medical problems, including sleep-disordered breathing (SDB). However, it has been measured in a few research studies as a training protocol to improve somatic motor function and increase growth factor expression in the central nervous system (Dale et al. 2014). Complication rates, cost, and QOL are among the many important factors to consider in all forms of assisted ventilation training.

Table 11. Intermittent Hypoxia

Author Year Country Research Design Score Sample Size	Methods	Outcome
Tester et al. 2014 USA Pre-post Level 4 N = 8	**Population:** 8 participants with incomplete SCI (4M 4F) Mean age (SD): 53.1(10.9) Mean DOI (SD): 5.1(1.7) years AIS-A/C/D: 1/2/5 6 cervical, 2 thoracic **Treatment**: 10 days of intermittent hypoxia. **Outcome Measures:** V_E, V_T, FVC, FEV_1, V_T, breathing frequency.	1. Significantly increased V_T during recovery in IH than that in sham protocol compared to baseline*. 2. Increased FVC and FEV_1 in 4 participants after 10 days, 3 showed no change, one showed decline. 3. Increase in MV significantly associated between increase in V_T & breathing frequency during recovery period after IH session. 4. No significant difference in MV, V_T, and breathing frequency in recovery periods and baseline* periods over 10 days of intervention, respectively. *values before each IH session, under supplemental CO_2.
Sankari et al. 2015 USA Cohort Level 2 N = 24	**Population:** 24 participants with SCI and SCI and non-SCI Mean age (SD): 38.9 (15.9) Mean DOI* (SD): 12.9 (6.2) AIS-A/C/D: 14/1/1 8 cervical SCI (CSCI), 8 thoracic SCI (TSCI), 8 non-SCI *Applicable to CSCI & TSCI groups only **Treatment**: Acute intermittent hypoxia (15 episodes of 1 min) & sham protocol on each participant. **Outcome Measures:** V_E, V_T, and cardiovascular measures	1. Significantly increased V_E during hypoxia. 2. Significantly increased V_E* in patients with cervical SCI only. 3. Significantly increased V_E variability* in patients with thoracic SCI only. 4. No significant change in V_E & V_E variability in sham protocols*. 5. Significantly higher V_E variability at baseline and recovery in patients with CSCI compared to TSCI and non-SCI. 6. Significantly increased V_T* in patients with CSCI & TSCI. 7. Significantly greater increase in V_T* in CSCI compared to TSCI. *During posthypoxic recovery compared to baseline.

Discussion

The study of Tester et al. (2014) compared intermittent hypoxia for 10 days (5 days/week) to a sham procedure in 8 patients with incomplete SCI. They showed evidence that acute exposure to intermittent hypoxia provides a significant increase in V_E for 30 min after the exposure, but not

after a sham exposure. However, the magnitude of ventilatory long-term facilitation was not enhanced over 10 days of exposure.

The study of Sankari et al. (2015) analyzed 8 patients with cervical SCI, 8 patients with thoracic SCI and 8 non-SCI participants who underwent acute intermittent hypoxia (15 episodes of 1 minute) or sham protocol. Patients with chronic SCI experienced a significant increase in V_E (only patients with cervical SCI) and V_T (most prominent in patients with cervical SCI, less prominent in those with thoracic SCI, and absent in non-SCI participants), compared with prehypoxia baseline levels, during the recovery phase after acute intermittent hypoxia.

However, Welch et al. (2021) found that acute intermittent hypoxia did not increase diaphragm PE_{max} amplitude or diaphragm compound muscle action potentials, and there was no evidence of diaphragm long-term facilitation. More research is needed before acute intermittent hypoxia could be recommended.

Conclusion

There is level 4 evidence (from one pre-post study: Tester et al. 2014) that the exposure to intermittent hypoxia during 10 days (5 days/week) provided short-term improvements in ventilation.

There is level 2 evidence (from one cohort study: Sankari et al. 2015) that the exposure to acute intermittent hypoxia increases the V_E (only in patients with cervical SCI) and V_T (significant increase in patients with cervical SCI), compared to prehypoxia baseline levels during the recovery phase after the exposure.

Key Points

Acute or midterm exposure to intermittent hypoxia could increase ventilatory parameters in patients with SCI in the short-term (within 30 minutes after hypoxic treatment).

More research is needed before intermittent hypoxia should be recommended.

11 Assistive Devices and Other Treatments

11.1 Girdle/Abdominal Binder

Abdominal binders are elastic/girdle type garments that are placed around the lower torso. They should be tight enough to provide support but not be uncomfortable. Abdominal binders are used mainly to improve breathing and circulation, help maintain balance and stability of the trunk, and to support sagging of the abdomen that can happen when abdominal muscles are weak (sometimes called ‘quad belly’). Abdominal binders are mostly used in people with loss of

abdominal wall strength (generally lesions above T6). Some early work (primarily level 4 studies) looking at the effects of abdominal binders on respiratory function in SCI was done prior to 1980 but was not included in this review. Studies on the effects of abdominal binders need to include positioning information as position greatly influences lung volumes in tetraplegia.

In addition to being used as a respiratory intervention, abdominal binders are used as an intervention in people with postural hypotension (see the Orthostatic Hypotension module).

Figure 7. Abdominal binders wrap around to support the abdomen when the abdominal muscles are weak or paralyzed. They are normally worn under the shirt

Table 12. Abdominal Binding

Author Year Country Research Design Score Sample Size	Methods	Outcome
Cornwell et al. 2014 Australia Cohort Level 2 N = 13	**Population:** 13 patients with acute traumatic motor-complete SCI from ICU (12M 1F) Mean age (SD): 36.9(21.8), lesion levels C3-T1. **Treatment:** AB, measurements taken while AB-on & AB-off for each patient. **Outcome Measures:** VC, FVC, FEV_1, PEFR, MEP, and various speech measures.	1. Significant increase in VC, FCV, & FEV_1 when AB is on, compared to when AB is off.
Wadsworth et al. 2012 Australia RCT (crossover) PEDro = 5 Level 2 N = 14	**Population:** 14 (13M; 1F) people with motor complete, C4-T1 SCI; mean (SD) age: 32(16)yrs. **Treatment:** AB on/off with participant seated in upright wheelchair, with 3 repeated measures at 6 weeks, 3 months, and 6 months after commencing daily use of an upright wheelchair. **Outcome measures:** FVC, FEV_1, PEFR, MIP, MEP, MAP, maximum sustained vowel time, sound pressure level.	1. AB significantly improved FVC (weighted mean difference .34L [95% confidence interval (CI) .10 –.58], *P*<.005), FEV_1 (.25L [.01-.51], *P*<05), PEFR (.81L/s [.13–1.48], *P*<.02), MIP (7.40cmH_2O [1.64 – 13.14], *P*<.01). 2. Participants stopped wearing an AB daily; reasons included "I think the AB will stop my abs from working" (n=2) and "the AB keeps riding up my ribs when I'm exercising" (n=1).
West et al. 2012 UK Pre-post	**Population:** 13 participants with SCI and 8 non-SCI matched-controls. *SCI group*:	1. In SCI, tight-bound increased VC (14%), expiratory flow throughout VC (15%), IC (21%),

Level 4 N = 21 (13 SCI)	12M 1F; mean(SD) age: 32(8). *Control group*: 6M 2F; mean(SD) age: 32(8) yrs. **Treatment:** Participants underwent three trials for assessment of: 1) diaphragm and ventilator function, 2) pulmonary function, and 3) cardiovascular function. For each trial, participants were exposed to 3 conditions: 1) unbound, 2) loose-bound and 3) tight-bound. **Outcome measures:** VC, expiratory flow, IC, maximal expiratory mouth pressure, RV, FRC, tidal and twitch transdiaphragmatic pressures, cardiac output, systolic mitral annular velocity, late-diastolic mitral annular velocity.	and MEP (25%). In contrast, tight-bound reduced RV (-34%) and FRC (-23%). 2. Tight-bound increased tidal and twitch transdiaphragmatic pressures (~45%). Tight-bound increased cardiac output (28%), systolic mitral annular velocity (22%), and late-diastolic mitral annular velocity (50%).
Julia et al. 2011 Malaysia Pre-post Level 4 N = 21	**Population:** 18M, 3F; 17 tetraplegia, 4 paraplegia; 13 complete, 8 incomplete. **Treatment:** Single-strap abdominal binder and triple-strap abdominal binder. **Outcome Measures:** Voluntary cough PEFR.	1. Both binders improved PEFR, but triple-strap abdominal binder improved to a greater extent. The difference in binder effects was significant for the tetraplegic group but not for the paraplegic group. 2. In participants with incomplete injury, PEFR increased from 290.0(105.8) L/min at baseline to 332.5(110.5) and 366.3(101.5) L/min with single-strap abdominal binder and with triple-strap abdominal binder, respectively.
Prigent et al. 2010 France Prospective observational Level 4 N = 72	**Population:** Regular corset users: 28 males, 8 females, mean age 37, mean YPI 7 Controls (no longer used corset): matched for sex and injury level; 28M, 8F, mean age 39, mean YPT 16. **Treatment:** use of corset. **Outcome measures:** VC, IC, Expiratory RV.	1. In supine, VC did not differ between users and nonusers, but in sitting, VC was less for the users without the corset than nonusers. Corset use increased VC in sitting. 2. 19 corset users compared at least 1 day with and without the corset during their usual activities and wearing the corset was associated with a significant drop in the severity of dyspnea.
Hart et al. 2005 France Pre-post Level 4 N = 10	**Population:** 7 tetraplegia, 3 paraplegia, mean age: 35.8 yrs, age range:18-56 yrs, 3-27 months post-injury, post-traumatic SCI levels: C5-T6, ASIA A. **Treatment:** Custom girdle, designed to provide truncal stability and abdominal support.	AB resulted in: 1. Decrease in respiratory effort measured by Borg scale (4.3(1.8) to 2.3(1.8)). 2. Increase in IC and FVC, 3. Decrease in FRC;

	Outcome measures: Spirometry.	4. Increase in diaphragm pressure-time product - a measure of diaphragm work; 5. Increases in twitch and maximal transdiaphragmatic pressure – measures of diaphragm force.
Estenne et al. 1998 USA Pre-post Level 4 N = 8	**Population:** 8 participants with SCI; Age range: 21-41 years; level of injury C5-C8; length of injury: 6-200 months **Treatment:** Abdominal strapping **Outcome measures**: Spirometry.	Strapping the abdomen in SCI resulted in: 1. Increase in VC; 2. Decrease in FRC and RV. 3. Small but inconsistent increases in maximal esophageal pressure (Pes) and expiratory flow rate that might not improve cough.
McCool et al. 1986 USA Prospective controlled trial Level 2 N = 13	**Population:** 13 tetraplegia (C4-C7), 9 non-SCI controls, all male, mean(SD) age: 29.9(11.4) yrs. **Treatment:** 3 Body Positions: supine, head-up tilted (37°) and seated – with and without abdominal binders. **Outcome measures**: Spirometry.	AB in SCI resulted in: 1. Increase IC in all positions, and TLC in the tilted and sitting positions. 2. Decrease in FRC in all positions. 3. An increase in rib cage dimensions at TLC.

Discussion

Studies demonstrate that abdominal binders in people with tetraplegia significantly increase IC or VC, and decrease FRC in all positions (McCool et al. 1986; Estenne et al. 1998; Hart et al. 2005; Prigent et al. 2010; Julia et al. 2011; West et al. 2012; Wadsworth et al. 2012). Wadsworth et al. (2012) showed that long-term use of AB significantly improved spirometry and inspiratory muscle strength. AB can improve PEFR (Wadsworth et al. 2012; West et al. 2012; Julia et al. 2011) but whether it can enhance or assist cough has been questioned (Estenne et al. 1998). Worthy of further study, the increase of diaphragmatic pressure-time product after AB may represent enhanced diaphragmatic force production, but it is not known if this change translates to an improved efficiency of breathing and decreased work of breathing.

Interventions to increase abdominal pressure and decrease the laxity of abdominal chest wall, which in turn affects diaphragm length and position, have been used in other patient groups. AB for people with SCI should be introduced cautiously and be rigorously assessed because of the potential for alteration of diaphragm length to result in mechanical inefficiency, increased dyspnea, and inspiratory muscle fatigue. The design of the abdominal binder may influence the impact of the abdominal binder (Julia et al. 2011).

One study has shown intermediate or long-term effects of AB on people with SCI (C4-T1). Positioning and using other interventions that increase abdominal pressure in other chronic respiratory conditions improve diaphragm force production but also can induce diaphragm fatigue and have variable influence on dyspnea reduction. The clinical outcomes of AB should be carefully evaluated for each person. AB could potentially have positive or deleterious effects on inspiratory muscle efficiency and dyspnea in different people after SCI.

Conclusion

There is level 2 evidence (Wadsworth et al. 2012; Cornwell et al. 2014) that AB in people with tetraplegia can improve respiratory function, and longer term use can continue to be effective.

Key Points

AB can be used to achieve immediate improvements in respiratory function, but long-term effects can be sustained during its application.

11.2Vibration

Vibration of the muscle tendon to enhance muscle contractile force has been studied in people with and without SCI. This modality may have the potential to decrease disuse atrophy in some people after SCI who have partial voluntary control of muscle and is described as being more comfortable than ES (Ribot-Ciscar et al. 2003). Alternatively, vibration also has been considered as an intervention to diminish involuntary muscle contraction after SCI (Butler et al. 2006). The literature on the use of vibration to improve inspiratory and expiratory muscle contraction or to control unwanted spasm of these muscles after SCI is almost non-existent. One early report examining the physiologic response to this modality in people with SCI is outlined in the following table.

Table 13. Vibration

Author Year Country Research Design Score Sample Size	Methods	Outcome
Homma et al. 1981 USA Pre-post Level 4 N = 13	**Population:** 13 people after SCI (11 M, 2 F), ages: 17-49 yrs, C4-T1 lesions, 1 incomplete, 12 complete); 19-49 months post-injury. **Treatment:** Application of vibratory stimulus to the 1) parasternal intercostal spaces; 2) 7th -10th intercostal spaces anterior to midaxillary lines; 3) Inspiratory and expiratory vibrations were combined to produce alternating in phase vibration. **Outcome measures:** Spirometry.	1. Inspiratory, expiratory, and combined in-phase vibrations increased V_T and V_E while decreasing fb. 2. The combined-alternating in-phase vibration increased V_T more than inspiratory or expiratory in-phase vibration alone.

Discussion

One report has shown that alternating in-phase vibration applied during inspiration (over the parasternal intercostals) or during expiration (applied over the 7^{th}-10^{th} intercostal spaces) significantly increased V_T and V_E with an even greater effect on these two variables when in-

phase vibration was applied during inspiration and expiration. Further study is required to examine the long-term utility and compliance of this modality to enhance ventilation in people with SCI. Further, the specific parameters of vibration that enhance vs. diminish muscle excitation and contraction needs to be explored in people with different levels and types of SCI.

Conclusion

There is level 4 evidence (from one pre-post study: Homma et al. 1981) that the use of chest wall vibration increases V_T and V_E in people with tetraplegia.

Key Points

Chest wall vibration may improve pulmonary function while the vibration is applied, but carry-over effects when the vibration is not in use have not been evaluated.

11.3Immersion

The effects of immersion in shoulder-deep water on spirometry in SCI have been studied. While immersion in water does not represent a treatment modality for pulmonary function, the effects of immersion are important to note from a clinical perspective because many people with SCI undergo pool-based therapy that exposes them to shoulder-deep immersion in water.

Table 14. Immersion

Author Year Country Research Design Score Sample Size	Methods	Outcome
Thomaz et al. 2005 Brazil Pre-post Level 4 N = 34	**Population:** 34 men: 23 complete (C4-C8) tetraplegia & 11 healthy controls. median age: 25yrs (treatment) & 27yrs (control), 2-89 months post-injury, AIS A-B **Treatment:** Spirometry immediately before and 5-15min following immersion to shoulder level in water (33.5°C-34.5°C) and 5-10min after withdrawal from the water. All participants were studied in upright, seated posture, in & out of the water. **Outcome Measures:** Spirometric measurements.	1. Immersion increased the FVC and FEV_1 of tetraplegic participants. FVC and FEV_1 decreased in control participants. 2. Among the participants with tetraplegia, the lower the pre-immersion VC, the greater the percentage of improvement following immersion. 3. No relationship was found between the time elapsed since cervical cord injury or its level and the degree of improvement.

Discussion

Immersion in shoulder-deep water results in changes in lung function tests in people with tetraplegia. Bosch and Wells (1991) showed that in comparison to able-bodied and people with paraplegia, people with tetraplegia have a significant decrease in residual volume (RV) with immersion. In a pre-post trial involving 23 motor complete people with tetraplegia and 11 healthy controls, Thomaz et al. (2005) concluded that overall, immersion in water appeared to improve breathing mechanics in people with tetraplegia.

Conclusion

There is level 4 evidence (from one pre-post study: Thomaz et al. 2005) that the use of immersion to shoulder-deep 33-34 °C water improves pulmonary function immediately in persons with tetraplegia but longer terms effects have not been evaluated.

Key Points

There is limited evidence that immersion to shoulder-deep 33-34° C water can improve pulmonary function immediately, but carry-over effects following immersion have not been evaluated.

12 Sleep-Disordered Breathing (SDB) in SCI

SDB, commonly known as sleep apnea, is a disease characterized by recurrent collapse of the upper airway during sleep leading to nocturnal hypoxemia and sleep fragmentation. Characteristic symptoms include loud snoring, excessive daytime sleepiness, and nocturnal choking. Risk factors for disease include alcohol use, sedatives, obesity, increased age, and male gender. Because of activation of systemic inflammation and the sympathetic nervous system, sleep apnea may be an independent risk factor for the development of cardiovascular disease. In the able-bodied, sleep apnea is relatively common and under-diagnosed.

Generally, the first line treatment of sleep apnea is lifestyle counseling (i.e., weight loss, avoidance of alcohol). There are different types of sleep apnea and they require different treatment approaches; obstructive sleep apnea (OSA) occurs when throat muscles relax, and central sleep apnea occurs when your brain does not send proper signals to the muscles that control breathing. OSA can be treated with continuous positive airway pressure (CPAP) therapy, considered to be first-line therapy. This consists of a mask placed on the face attached to an air compressor via plastic tubing. CPAP devices establish a positive pressure in the upper airway preventing its collapse during sleep. Studies of CPAP in people without SCI demonstrate significant benefits in terms of reducing sleepiness and preventing motor vehicle crashes. Other therapies that have been used to treat OSA include mandibular advancement devices (dental splints) and upper airway surgery. Central sleep apnea requires a back-up rate, and sleep-related hypoventilation and a pressure differential between inspiration and expiration (a treatment

called Bi-level PAP) (Chiodo et al. 2016). Research shows that central apnea is more common in patients with tetraplegia than in patients with paraplegia (Chiodo et al. 2016).

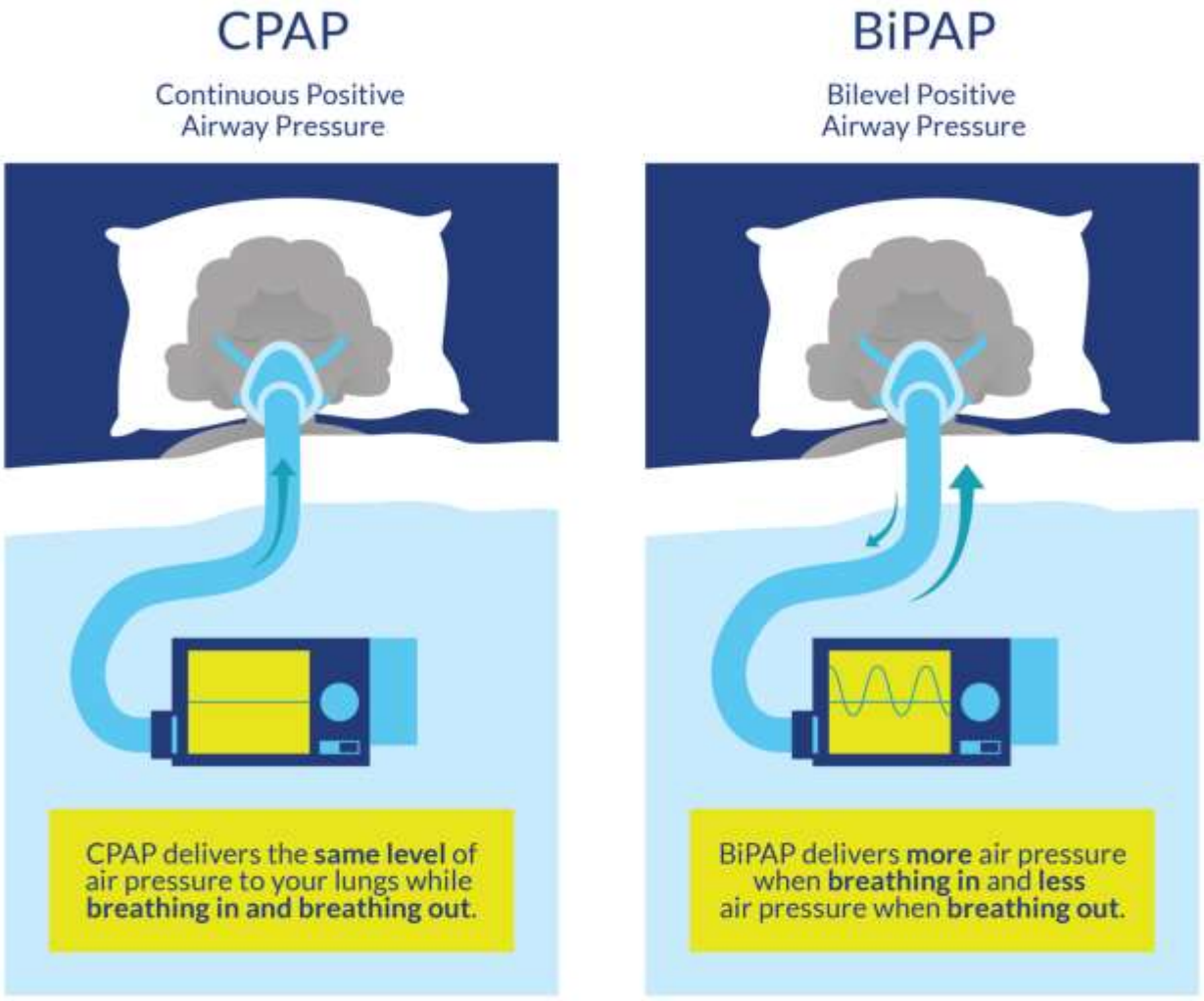


Figure 8. Description of the BiPAP and CPAP systems, designed for non-invasive respiratory pressure support

12.1Prevalence and Risk Factors

Breathing disorders including sleep apnea appear to have a higher prevalence in people after SCI than those without with some researchers estimating it is present in 60% of motor complete persons with tetraplegia (Prosperio et al. 2015; Chiodo et al. 2016). In general, the studies that examined the prevalence of OSA were limited by small sample sizes and by an experimental design that lacked a non-SCI control group that could be directly compared to the patients with SCI. Both overnight oximetry and full polysomnography (PSG) were used to diagnose disease. The prevalence rate ranged from 9.1-83% (Short et al. 1992; Burns et al. 2000; Burns et al. 2001;

Stockhammer et al. 2002; Berlowitz et al. 2005). Obesity was identified as a risk factor for sleep apnea in most studies. The use of muscle relaxants was identified as a potential risk factor for SDB in some but not all studies (Short et al. 1992; Ayas et al. 2001; Burns et al. 2001; Berlowitz et al. 2005).

Table 15. Treatment of Sleep Disordered Breathing

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Wijesuriya et al. 2019 Australia RCT (crossover) PEDro = 8 Level 1 N = 12	**Population:** 12 male patients with chronic SCI; tetraplegia; AIS A (n = 9) or B (n = 3); mean (SD) age 52.1 (± 12.1) years; level of injury C4 (n = 3), C5 (n = 5), and C6 (n = 4); mean (SD) time since injury 22.3 (± 15.7) years; and OSA. **Treatment:** Two study visits were carried out in the participants' homes, with a 1-week washout period. At each visit, nasal spray (0.5 mL of 5% phenylephrine (PE) or placebo) was administered. **Outcome Measures:** Nasal resistance; overnight polysomnography (PSG) (apnea hypoapnea index, total sleep time, route of breathing, arousal index, 4% O_2 desaturation index, slow wave, and rapid eye movement (REM) sleep percentages, overnight respiratory and sleep events); and perceived nasal congestion (Borg-like scale of Nasal Obstruction and Congestion Quantifier five-item test).	1. Nasal resistance was reduced by 72% following administration of PE (p = 0.02; mean difference −5.20: 95% confidence interval −9.09, −1.32 $cmH_2O/L/s$). 2. No significant treatments effects were observed for apnea hypoapnea index, total sleep time, REM sleep time, arousal index, 4% O_2 desaturation index or route of breathing (in the first half of the night, or the full night) between nights where PE or placebo were administered. 3. Self-reported nasal blockage (p = 0.09; −0.88 (−2.09, 0.34) and the rate of obstructive apneas per hour (p = 0.15; −6.37 (−33.31, 20.58) were not significantly reduced following PE while overnight slow wave sleep was not significantly increased (p = 0.07; 9.88 (−4.30, 24.07)). 4. Raw PSG data demonstrated changes in sleep architecture and respiratory event severity with PE administration at an individual participant level. Nasal decongestion in all but one of the participants reduced respiratory event severity (apneas fell and hypopnoeas rose). The reduction in respiratory event severity with PE was not statistically significant (p = 0.28; mean difference −9.7%: 95% confidence interval −28.5, 9.1).

Maresh et al. 2020 USA RCT (crossover pilot) PEDro = 6 Level 2 N = 8	**Population:** 8 non-ventilator-dependent males with chronic SCI; mean (SD) time since injury 9.5 (± 8.5) years; mean (SD) age 47.6 (± 13.8) years; level of injury cervical (n = 5), and thoracic (n = 3); AIS A (n = 4), AIS B (n = 2), AIS C (n = 2); and sleep-disordered breathing (SDB) (AHI ≥ 5 events / h). **Intervention:** Each participant went on Trazodone (100 mg), Buspirone (30 mg), and placebo for 2 weeks each, with a washout period of ≥ 2 weeks. **Outcome Measures:** Overnight in-laboratory PSG, and induction of central sleep apnea using NIV or hypercapneia protocol. Indexes of SDB, CO_2 reserve, apneic threshold, hypocapnic chemoreflex sensitivity or controller gain, plant gain, and ventilatory parameters (V_E, V_T, breaths/min, MIP, inspiratory duration, expiratory duration, breath duration, fractional inspiratory time, $P_{ET}O_2$, $P_{ET}CO_2$, and oxyhemoglobin saturation) were assessed on a night study on day 13 of being on each medication.	1. CO_2 reserve was widened significantly on Buspirone compared with placebo (-3.6 ± 0.9 vs. -1.8 ± 1.5 mmHg, respectively, *P* < 0.001), and with Trazodone (-3.6 ± 0.9 vs. -2.5 ± 1.0 mmHg, respectively, *P* <0.009) but not on Trazadone compared with placebo (-2.5 ± 1.0 vs. -1.8 ± 1.5 mmHg, respectively, *P* = 0.061). 2. There were no significant changes in apneic threshold $P_{ET}CO_2$, and eupneic CO_2. 3. Buspirone significantly decreased controller gain compared with placebo (1.8 ± 0.4 vs. 4.0 ± 2.0 L/(mmHg· min) respectively, *P* = 0.025) but not Trazodone compared with placebo (2.5 ± 1.1 vs. 4.0 ± 2.0 L/(mmHg·min) respectively; *P* > 0.05). 4. Plant gain was not significantly different for either Buspirone (5.6 ± 1.1 mmHg·min/L, *P* > 0.05) or Trazodone (6.5 ± 2.0 mmHg·min/L, *P* > 0.05) compared with placebo (5.1 ± 1.7 mmHg·min/L). 5. There were also no significant differences between any of the interventions for apnea hypoapnea index, the central apnea index, obstructive apnea index, or oxygen desaturation index between groups.
Ginter et al. 2020 USA RCT (crossover) PEDro = 6 Level 2 N = 16	**Population:** 16 participants with evidence of SDB (apnea-hypopnea index ≥ 5 events/hour). Participants with SCI (n = 8): 7 males and 1 female; age 50.3 ± 12.8 years; SCI level cervical (n = 7), and thoracic (n = 1); ASIA A (n = 1), ASIA B (n = 2), ASIA C (n = 1) and ASIA D (n = 4); and mean (SD) time since injury 8.3 (± 4.7) years. Non-SCI participants (n = 8): 6 males and 2 females; age 59.5 ± 11.8 years. **Intervention:** Participants were randomized to receive oral acetazolamide (ACZ) 500 mg or	1. Ventilatory parameters remained similar after placebo or ACZ except for total CO_2, which was lower after ACZ compared to placebo in both groups of participants (p < 0.05). 2. Treatment with ACZ for three days resulted in widening of the CO_2 reserve (-4.0 ± 1.2 vs. -3.0 ± 0.7 mmHg for non-SCI, -3.4 ± 1.9 vs. -2.2 ± 2.2 mmHg for SCI, *P* < 0.0001), and a corresponding decrease in the hypocapnic apnea threshold (28.3 ± 5.2 vs. 37.1 ± 5.6 mmHg for non-SCI, 29.9 ± 5.4 vs. 34.8 ± 6.9 mmHg for SCI, *P* < 0.0001), respectively.

	placebo twice a day during a 3 days period. After completing the first drug arm, participants underwent a 1-week washout period before crossing over to the other drug arm. **Outcome Measures:** Study nights (at 3 night of intervention) included PSG and determination of the hypocapnic apneic threshold and CO_2 reserve using NIV. For participants with spontaneous central apnea, CO_2 was administered until central apnea was abolished, and CO_2 reserve was measured as the difference in $P_{ET}CO_2$ before and after. Steady-state plant gain (the response of end-tidal PCO_2 to changes in ventilation) was calculated from $P_{ET}CO_2$ and V_E ratio during stable sleep. Controller gain (the response of ventilatory drive to changes in end-tidal PCO_2), was defined as the ratio of change in V_E between control and hypopnea to the ΔCO_2 during stable non-REM sleep. The change in sleep parameters (apnea-hypopnea index, central apnea index, oxyhemoglobin desaturation index, respiratory effort-related arousal index, periodic leg movement arousal index, and sleep efficiency), and ventilatory and physiological parameters (V_T, V_E, respiratory rate, inspiratory durations, expiratory duration, breath duration, and oxyhemoglobin saturation and $P_{ET}CO_2$) were also collected.	3. ACZ significantly reduced plant gain when compared with placebo (4.1 ± 1.7 vs. 5.4 ± 1.8 mmHg/L min for non-SCI, 4.1 ± 2.0 vs. 5.1 ± 1.7 $mmHg \cdot L^{-1} \cdot min$ for SCI, $P < 0.01$). → Decreases susceptibility to hypocapnic central apnea. 4. ACZ significantly reduced controller gain when compared with placebo in the SCI group (2.1 ± 0.7 vs. 2.8 ± 1.3 $L \cdot min^{-1} \cdot mmHg^{-1}$) and the non-SCI group (2.2 ± 0.5 vs. 2.6 ± 0.6, $P = 0.01$). 5. Peripheral hyperoxic exposure resulted in a significant decrease in V_E in both groups ($F = 86.75$, $P < 0.0001$) for both the placebo and acetazolamide arms. There was no significant interaction between the groups and drug arms. 6. ACZ decreased apnea-hypopnea index (28.8 ± 22.9 vs. 39.3 ± 24.1 events/h; $P = 0.05$), central apnea index (0.6 ± 1.5 vs. 6.3 ± 13.1 events/h; $P = 0.05$), and oxyhemoglobin desaturation index (7.5 ± 8.3 vs. 19.2 ± 15.2 events/h; $P = 0.01$) compared with placebo; in contrast, periodic leg movement arousal index was slightly increased on ACZ compared with placebo (1.1 ± 1.7 vs. 0.3 ± 0.5 events/h, respectively, $F = 3.07$, $P = 0.05$); and ACZ use was not associated with significant differences in sleep efficiency or respiratory effort-related arousal index. 7. Although further investigation in a larger sample of patients is required; ACZ may attenuate central sleep apnea and improve nocturnal O_2 saturation.
Brown et al. 2018 USA Cohort Level 2 N = 91	**Population:** 91 participants with SCI and SDB; 75 males and 16 females; mean (SD) age 48 (± 12) years; mean (SD) time since injury 17 (± 12) years; motor levels C1-C3 (4%), C4-C6 (59%), C7-C8 (12%), and T-level (26%). 74/91 participants underwent home sleep apnea test and SpO_2/tc-pCO_2 testing showing:	1. Overall, 45% of 91 participants completed the study. 2. There was great diversity among patients with SCI in PAP utilization. 3. At 3 months (55/91) 38% of participants were high-level users (87 ± 12% nights, 374 ± 115 min per night; mean ± SD), 20% were medium- level users (35 ± 16%

	● 81% had evidence of OSA (50% mild, and 50% moderate or severe); of the anormal studies, there were a median of 12.4 obstructive events per hour. ● 28% had hypercapnia; in the abnormal studies, hypercapnia was present for 25% of the study time. **Intervention:** Based on SDB assessment (home sleep apnea test combined with overnight oxygen saturation (SpO_2)/transcutaneous pCO_2 (tc-pCO_2)), participants received different interventions: ● Participants diagnosed with nocturnal hypercapnia were prescribed bi-level positive airway pressure-average volume-assured pressure support (BiPAP-AVAPS; this device maintains the programmed EPAP and auto-titrates the IPAP to achieve the target average V_T). ● Participants with SDB but no hypercapnia were started on bi-level positive airway pressure-Auto (BiPAP-Auto; this device auto-titrates the EPAP to control apneic events, and the IPAP to control hypopneas). ● Participants without SDB were not prescribed a positive airway pressure (PAP) device but completed symptom logs and questionnaires. **Outcome Measures:** Adherence, daily event logs (to record episodes with symptoms of autonomic dysfunction, RI, and episodes of mucus plugging/atelectasis), SF-12v.2, Brief Pain Inventory-SF, Epworth Sleepiness Scale, and adherence (high-level use defined as ≥ 70% nights used and ≥ 240 min per night; medium-level use defined as ≥ 15% nights used and ≥ 60 min per night but less than high-level users; and low-level use defined by < 15% nights used or < 60	nights, 144 ± 68 min per night), and 42% were low-level users (9 ± 9% nights, 85 ± 77 min per night). PAP therapy was effective in improving OSA in 89% and nocturnal hypercapnia in 77%. 4. Higher PAP pressures predicted higher levels of device use; at month 3: a. In participants prescribed BiPAP-Auto, average EPAP had significant predictive value for both % days used and minutes per night ($p = 0.04$) and % days used ($p = 0.04$). b. For participants prescribed BiPAP/AVAPS, average IPAP had significant predictive value for both minutes per night used ($p = 0.014$) and % days used ($p = 0.048$). c. By the other hand, SCI level or SDB severity were not predictors of device use ($p = 0.7$ and $p = 0.8$, respectively). 5. There were marked reductions in symptoms of autonomic dysreflexia ($p = 0.01$) and orthostatic hypotension ($p = 0.1$) as well as some improved indices of QOL; but larger cohorts in each user group would be necessary to describe and relationship between PAP use and effects on these outcomes.

	min per night) through PAP device data were collected at month 0, 3, 6 and 12 of the beginning of the study.	
Graco et al. 2019 Australia Pre – post Level 4 N = 16	**Population:** 16 patients with traumatic cervical SCI, OSA; mean (SD) age 56.3 (± 15.5) years; 13 males and 3 females; 21.0 (± 14.9) years since injury; C1-C4, AIS A, B, C (n = 1), C5-C8, AIS A, B, C (n = 13); T1-S3, AIS A, B, C (n = 0); AIS D, at any level (n = 2); C1-C4 (n = 1); C5-T1 (n = 15); and AIS A (n = 4). **Intervention:** Auto-titrating CPAP and supported for 1 month. **Outcome Measures:** Participants completed an in-depth semi-structured interview, the Karolinska Sleepiness Scale, and a seven-item CPAP adverse events questionnaire at one, six and 12 months.	1. At one month, mean nightly CPAP use was 3.1 h, with 38% achieving at least 4 h per night. Mean nightly use dropped to 2.6 h at 6 months and 2.1 h at 12 months, with one quarter of the sample achieving at least 4 h per night in these time periods. 2. Between months one and six, two patients became adherent and four became non-adherent. No participant changed adherent status after six months. By 12 months CPAP usage was distinctly bi-model and stable, with either high usage (> 6 h per night) or low usage (< 3 h per night). 3. CPAP use (average nightly hours) at 6 and 12 months were strongly associated with more hours spent with the sleep scientist in the first month and greater years since injury ($p < 0.05$). 4. Mean Karolinska Sleepiness Scale score at baseline was 4.3 (± 2.1) and at 1 month review was 2.9 (± 2.1). 5. Qualitative results of interviews showed that all participants experienced burdens and adverse events from using CPAP, and the trade-off between the perceived burden and the perceived benefit appeared to impact adherence to the therapy.
Sankari et al. 2014 USA Prospective observational Level 4 N = 24	**Population:** Twenty-four participants (8 cervical SCI, 8 thoracic SCI, and 8 controls – 3 females, 5 males in each group) mean (SD) BMI: 29.2(6.6) kg/m2; most of whom were diagnosed with sleep apnea. **Treatment:** None. **Outcome Measures:** The ventilation, timing, Upper Airway resistance,	1. Compared with controls, both cervical and thoracic SCI participants demonstrated elevated passive critical closing pressure. 2. No difference in upper airway resistance was observed between groups. Participants with cervical and thoracic SCI had a similar degree of hypoventilation and

	and pharyngeal collapsibility, defined by critical closing pressure, were determined during non-REM sleep. Inspiratory duty cycle and V_E were observed in response to increasing severity of upper airway obstruction.	dose- dependent increase in inspiratory duty cycle in response to upper airway obstruction. 3. Passive upper airway collapsibility is increased in both cervical and thoracic SCI compared with controls. 4. The neuromuscular compensatory responses to upper airway obstruction during sleep are preserved in chronic SCI and are independent of the level of injury.
Burns et al. 2005 USA Case series Level 4 N = 40	**Population:** 40 men after SCI (37 with tetraplegia) Mean (SD) BMI: 29.2(6.6) kg/m^2; most of whom were diagnosed with sleep apnea. **Treatment:** None. **Outcome Measures:** Survey requesting information about long-term treatment outcomes and side effects of sleep apnea treatment in persons with SCI.	1. CPAP continually used by 63% of the participants out of 32 (80%) of participants who tried it. 2. Main reasons for not using CPAP were inability to fall sleep, mask discomfort & claustrophobia. 3. Most common side effects were nasal congestion in 12 and mask discomfort in 8.
Stockhammer et al. 2002 Switzerland Pre-post Level 4 N = 50	**Population**: 50 people (40M 10F) with SCI lesion levels between C3 and C8; mean(SD) age: 48.6(14.0), range from 20- 81 years; Mean 11.4 years post injury (range from 0.5 to 37 years) . **Treatment:** CPAP. **Outcome Measures:** Sleep breathing data and oxymetric values were investigated in context with age, gender, BMI, neck circumference, type and height of lesion, time after injury, spirometric values and medication. A non-validated short questionnaire on daytime complaints was added.	1. 31 out of the 50 participants with tetraplegia had a respiratory disturbance index of 15 or more (mean 30.5) defined as SDB. 2. 16 patients accepted a trial of CPAP; of these, 11 continued to use CPAP after a few weeks. Of these 11 patients, 10 patients reported an improvement of symptoms after using long term CPAP therapy.
Biering-Sørensen et al. 1995 England Case series Level 4 N = 3	**Population**: 3 people after SCI, ages: 47, 54, 56 yrs, C6 incomplete, T2 complete; Duration of injury: 19, 6, 37 years. All 3 patients reported severe daytime fatigue and sleep complaints. **Treatment:** CPAP via a nasal mask. **Outcome Measures:** Case report for each patient; measures included PSG.	1. In two patients, CPAP treatment decreased daytime sleepiness, improved sleep and oxygen saturation. 2. One patient improved after losing 33 kg, reducing alcohol intake and quitting smoking.

Discussion

SDB is common in people with SCI; obesity appears to be a consistent risk factor. There are few studies that have assessed the impact of sleep apnea therapy in patients with SCI.

Burns et al. (2005) demonstrated a long-term acceptance rate of CPAP of 63% (20/32) in patients offered CPAP therapy, and Stockhammer et al. (2002) reported that of the study participants that continued with longer-term usage of CPAP (10/16, 62.5%) experienced it as beneficial. Discontinuing use of CPAP was generally attributed to the discomfort of wearing a mask to sleep or feelings of claustrophobia (Burns et al. 2005). A limited number of studies have examined the impact of sleep apnea therapy on health and QOL outcomes in SCI; future investigations should examine these and other questions with larger sample sizes to determine more accurate effects of CPAP therapy.

A few studies with small sample sizes assessed the use of medications in patients with SCI for SDB. Two RCTs (Maresh et al. 2020; Ginter et al. 2020) found that Buspirone or acetazolamide widened the CO_2 reserve and hence decreased susceptibility to hypocapnic central apnea more than a placebo. However, both studies also showed limited effects of these medications on other respiratory parameters of SDB. Wijesuriya et al. (2019) also showed no significant differences on components of SDB with the administration of a phenylephrine nasal spray, other than a 72% decrease of nasal resistance. Additional RCTs with groups of at least 20 participants or more will be required to determine if any of these medications can have significant effects on sleep quality, rapid eye movement (REM) sleep time, or if they can make any other improvements on people with SDB.

Conclusion

There is level 1 evidence (from two RCTs: Maresh et al. 2020; Ginter et al. 2020) that medication such as Buspirone or acetazolamide, expands the CO_2 reserve and hence decreases susceptibility to hypocapnic central apnea more than a placebo but does not show effects in other respiratory parameters of SDB in people with SCI.

There is level 1 (from one RCT: Wijesuriya et al. 2019) that administration of a phenylephrine nasal spray provides a 72% decrease of nasal resistance without additional effects in other clinical components of SDB in people with SCI.

There is level 4 evidence (from two case series and two pre-post studies: Stockhammer et al. 2002; Burns et al. 2005; Biering-Sørensen et al. 1995; Yang et al. 2014) to support CPAP therapy to treat SDB in people with SCI.

Key Points

People with SCI have a high prevalence of SDB, and therapy may improve QOL and other outcomes. Therefore, we recommend vigilance for suggestive signs and symptoms (e.g., snoring, obesity, witnessed apneas, daytime sleepiness) and further testing in patients with suggestive symptoms/signs (with overnight oximetry or PSG).

13 Cough Assist and Secretion Removal

People with SCI are at risk for retention of secretions because of an increased prevalence of pneumonia compounded by lower expiratory flows during cough, which is greatest during the acute phase after SCI. Increased prevalence of RI, although decreased during the rehabilitation phase of recovery, is still higher in people with SCI compared to age-matched healthy people, and secretion retention is a major contributor to respiratory illness in people with SCI (Reid et al. 2010). Reduction in expiratory flows during cough is related to the higher levels of SCI. Of considerable surprise, several devices that have been shown to be effective in people with other chronic respiratory conditions have not been evaluated in people with SCI.

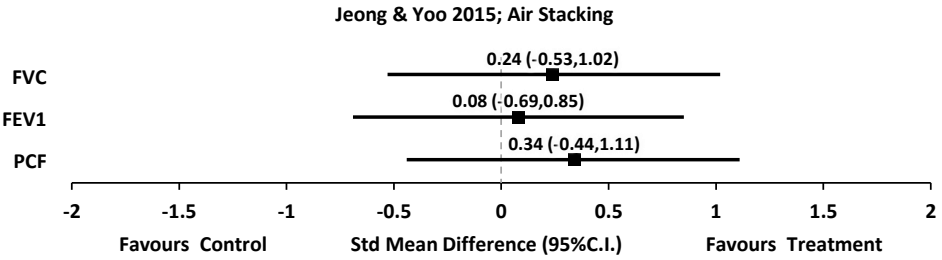
Table 16. Cough Assist and Secretion Removal

Author Year Country Research Design Score Sample Size	Methods	Outcome
DiMarco et al. 2019 USA Pre – post Level 4 N = 3	**Population:** 3 male patients with SCI who were being ventilated with a DPS to support ventilation, mean age 35 years, ASIA A (n = 2) and ASIA B (n = 1). **Treatment:** Patients received spinal cord stimulation (SCS) to restore expiratory muscle function and cough. SCS had to be applied every 30 s for 5–10 min, 2 or 3 times/ day, and during evacuation of secretions or airway clearance, as needed. Stimulus parameters were set at values resulting in maximal PAP generation. **Outcome Measures:** PE_{max}; PEF and airway pressure generation during SCS after pacing volume	1. At baseline, when participants assisted the pacing system by making a maximal inspiratory effort synchronized with the paced breath, inspired volumes increased to 1.5 ± 0.1 L when participants made maximum inspiratory and expiratory efforts synchronized with DP, mean PEF and PE_{max} were 2.2 ± 0.2 L/s and 39 ± 6 cmH_2O, respectively. 2. After a mean of 16.0 ± 5.9 weeks after initiation of SCS: With maneuver #1, PEF and PE_{max} were 3.7 ± 0.4 L/s and 56 ± 3 cmH_2O respectively ($P < 0.05$ for both when compared with unassisted efforts). With maneuver #2, PEF and PE_{max} were 7.5 ± 1.5 L/s and 75 ± 4 cmH_2O respectively ($P < 0.05$ for both

	(maneuver #1), SCS after pacing volume and participant maximal spontaneous inspiratory effort (maneuver #2), and SCS after pacing volume and participant maximal spontaneous inspiratory with maximal spontaneous expiratory effort (maneuver #3); and a short questionnaire (an assessment of the degree of difficulty in raising secretions) were assessed every 4-5 weeks for an approximately 6-month period post implantation.	when compared with maneuver #1). With maneuver #3, PEF and PE_{max} were 9.0 ± 1.9 L/s and 90 ± 6 cmH_2O respectively (P < 0.05 when compared with maneuvers #1 and #2). 3. At the 20-, 24-, and 28-week after implantation, participants reported substantial improvement reporting none to only mild difficulty. With regard to ease in raising secretions with use of the cough system compared with other methods, there was also marked improvement in each person at each of the three time points. 4. 2/3 participant developed asymptomatic signs of autonomic dysfunction. No other side effects were noted.
DiMarco et al. 2020 USA Pre – post Level 4 N = 10	**Population:** 10 male patients with cervical SCI and marked paresis of their expiratory muscles, mean age 40 years, and 7 years post injury. **Treatment:** SCS (this device involves the minimally invasive placement of wire electrodes on the dorsal epidural surface of the spinal cord at the T9 and T11 levels). Participants were instructed to use SCS every ~30s for 5– 10 min, 2–3 times/day and as needed to clear airway secretions. Stimulus parameters were set at values (30–40 V, 50 Hz, pulse width 0.2ms) which resulted in near maximal PAP generation. **Outcome Measures:** Spontaneous IC, PI_{max}, PE_{max} and maximum airway pressure generation during SCS at TLC with individual maximal expiratory effort, were measured at baseline and over a 20-week period.	1. Each study participant used SCS on a regular, daily basis. 2. Lung function increased gradually from over the course of the study. By week #20, mean IC and PI_{max} had increased by 127 ± 8% (P < 0.05) and 127 ± 6% (P < 0.05), respectively. By the other hand, spontaneous PE_{max} increased 127 ± 14% of baseline values but without reaching significance (P > 0.05). 3. At week #20, the magnitude of airway pressure generation during SCS with patient effort at TLC was linearly related to IC and PI_{max} with correlation coefficients of 0.72 (P < 0.05) and 0.82 (P < 0.05), respectively.
DiMarco et al. 2021 USA Pre – post Level 4 N = 5	**Population:** 5 male patients with cervical SCI, mean age 37 years, AIS A (n = 5), time since injury 3 years. **Intervention:** Fully implantable lower thoracic SCS cough system	1. Consequent to muscle reconditioning, daily use of SCS resulted in the gradual increase in airway pressure generation over the course of the initial 4-17 weeks after which this parameter plateaued. Measured with 40-V stimulation (50Hz,

	was surgically placed to improve bowel management. SCS was applied at home, every 30 s for 5-10 min. Participants used the device 2-3 times/d, on a chronic basis to maintain expiratory muscle strength; for evacuation of secretions or airway clearance as needed; and during bowel routines at their discretion during a 21-week period. For each participant stimulus parameters were set at values resulting in maximal airway pressure generation. **Outcome Measures:** Airway pressure generation (achieved spontaneously, and with SCS at FRC, TLC and TLC with maximal expiratory effort), and weekly completion of Bowel Routine Log (including bowel management, medications taken, use of mechanical methods, frequency of bowel-related activities, and use of SCS) were collected at week 0 (first day of stimulation) and at weeks 4, 8, 12, 17, and 21 after initiation of SCS.	0.2ms pulse width), airway pressure increased during SCS at FRC, TLC, and TLC with maximum expiratory effort. As expected, pressure generation increased with increasing stimulus amplitude between 10 and 40 V after the reconditioning period.
DiMarco et al. 2022 USA Pre – post Level 4 N = 29	**Population:** 29 patients with traumatic SCI and significant paresis of their expiratory muscles, 26 males and 3 females, mean age at implantation 42.5 years, ASIA A (n = 28) and ASIA B (n = 1); and mean time since injury 10 years. **Treatment:** Patients received SCS and were divided in two groups according with the type of the electrodes used (wire electrodes (WE), n = 12; and disc electrodes (DE), n = 17). Electrodes were implanted between T9 and T11 spinal levels; total duration of stimulation ranged between 0.6 and 0.8 s and pulse duration was 0.2 ms; and stimulus frequency was set at 50 Hz. Participants were instructed to apply stimulation every 30 s for 5 – 10 min, 2 or 3	1. Following the reconditioning program, with both types of electrodes, SCS (at FRC, TLC, and TLC with individual effort) resulted in substantial increases in airway pressure and peak airflow compared to spontaneous efforts ($P < 0.05$). There was no significant difference between use of the DE vs. the WE. 2. There were linear relationships between airway pressure and peak airflow for both types of electrodes (with no significant differences between DE and WE). 3. Following use of SCS, the need for suctioning or assisted cough fell to 0.56 ± 0.20 and 0.55 ± 0.21 for DE and WE, respectively representing unaware or rare need for use of these maneuvers comparing with baseline ($P < 0.05$ for each).

	times/day, and when, as required, for evacuation of secretions. **Outcome Measures:** Airway pressure and peak airflow generation achieved with SCS; clinical parameters including ease in raising secretions, incidence of acute respiratory tract infections (RTI) and side effects were collected at baseline and during outpatient visits every 4–5 weeks during the first 28 weeks, then at 3-month intervals for 6 months, and after 1 year.	4. The number of RTI fell from an average of 1.3 ± 0.3 and 1.3 ± 0.5 / year to 0.3 ± 0.1 and 0.1 ± 0.1 / year for the DE and WE, respectively ($P < 0.01$ for each). 5. The only significant side effect was the occurrence of autonomic dysfunction which occurred in 11 of the 29 patients; 5 in the DE and 6 in the WE groups ($P > 0.05$).
Nygren-Bonnier et al. 2018 Sweden Pre – post Level 4 N = 20	**Population:** 10 ventilatory independent patients with SCI; mean time since injury 20.5 (5-42) years; 9 males and one female; mean age 42.5 (24-64) years; C5 AIS B (n = 1), C6 AIS A (n = 5), C6 AIS B (n = 2), C7 AIS B (n = 1), and C8 AIS B (n = 1). 10 participants able to perform glossopharyngeal insufflation (GI) acted as reference group. **Intervention:** Performing the glossopharyngeal breathing procedure in a single session. **Outcome Measures:** TLC, VC, RV, PCO_2, PO_2, mean arterial blood pressure, mouth airway pressure and HR were collected in a sitting position at baseline, in a sitting position with GI, in a supine position with GI, and finally in a sitting position after the intervention.	1. Comparing to baseline, the non-SCI group (with respect to the SCI group) performing GI in a sitting position had a higher increase in TLC ($P < 0.01$), VC ($P < 0.001$), Paw ($P < 0.001$), and HR ($P < 0.05$), a higher decrease in MAP ($P < 0.001$), and there was no difference in RV. 2. While performing GI in a sitting compared to a supine position, TLC, mean arterial blood pressure, HR, and mouth airway pressure remained unchanged in the SCI group whereas RV decreased in the supine position ($P < 0.01$). The difference in RV in a sitting compared to a supine position also differed between the groups ($P < 0.01$) and the able-bodied group had a higher HR in a sitting position compared to the SCI group, ($P < 0.01$). 3. Mean arterial blood pressure, HR, and mouth airway pressure responded in similar way in both groups in a sitting as well as a supine position.
Molgat-Seon et al. 2017 Canada Pre – post Level 4 N = 12 (2 with cervical SCI)	**Population:** 12 people with respiratory muscle weakness (maximal inspiratory mouth pressure <30% predicted; age = 29 ± 3 yrs), including 2 with C5 SCI, and 12 healthy controls (age = 29 ± 2 yrs) **Treatment:** LVR with manual resuscitation bag delivered to maximum tolerated mouth pressure.	1. In the respiratory muscle weakness group, LVR increased respiratory system compliance 40% above baseline, no change in control group. 2. Peak expired flow during LVR increased ~1l/s 3. No change in unassisted PEF or PCF. 4. LVR had no effect on lung volumes.

<table>
<tr><td></td><td>Outcome Measures: Maximum insufflation capacity; respiratory system compliance (pulse method); PCF; PEF during LVR; lung volumes (TLC, VC, IC, FRC, ERC, RV).</td><td></td></tr>
<tr><td rowspan="2">Jeong & Yoo 2015
Korea
RCT
PEDro = 6
Level 1
N = 26</td><td>Population: 26 participants with cervical SCI
Mean (SD) age*: 47.6 (11.7) years
*data prior to exclusion, N=30
Treatment: Experimental group (14, Exp): 20 repetitions of air stacking twice a day
Control group (12, Ctrl): 20 repetitions of incentive spirometry twice a day.
Outcome Measures: FVC, FEV_1, PCF.</td><td>1. Between-group – significant increase in FVC and PCF in experimental group compared to controls.
2. Within-group – significant difference in FVC and PCF at 6 weeks (compared to baseline) in experimental group; only FVC significantly different at 6 weeks in controls.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data.
 
</td></tr>
<tr><td>Torres-Castro et al. 2014
Chile
Cross-sectional
Level 5
N = 15</td><td>Population: Fifteen in-patients with complete tetraplegia (C4–C6, AIS A) were included. Median age was 33 years (16–56).
Treatment: PCF was measured during four different interventions: spontaneous maximal expiratory effort (MEE); MEE while receiving Assisted Cough (MEE-AC); MEE after Air Stacking with a manual resuscitation bag (AS-MEE); and MEE with AS and AC (AS-MEE-AC).
Outcome Measures: PCF.</td><td>1. We observed significant differences in PCF while applying MEE-AC and AS-MEE compared with MEE.
2. The difference in PCF value was greatest using the AS-MEE-AC techniques combined.
3. The application of combined techniques (AS-MEE-AC) can reach near normal PCF values. This is a low-cost, simple and easily applied intervention that could be introduced to all patients with tetraplegia.</td></tr>
<tr><td>Pillastrini et al. 2006
Italy
RCT
PEDro = 3
Level 2</td><td>Population: Complete cervical SCI, control group mean(SD) age 52.2(17.6) yrs; experimental group age 31.5(16.1) yrs. Number of participants not reported.</td><td>1. Experimental group showed significant increases in FVC, FEV_1 and PEF.
2. Use of MIE is shown to be an effective adjunct to manual chest therapy techniques, since it makes it possible</td></tr>
</table>

N = not reported	**Treatment:** Experimental group = Manual respiratory kinesitherapy (included chest therapy techniques such as postural drainage, assisted coughing, Ambu bag to provide positive pressure) coupled with MIE (portable machine which inflates lung with positive pressure and assists coughing with negative pressure); control group = manual kinesitherapy only. **Outcome Measures:** FVC, FEV_1 and PEF.	to achieve adequate bronchio-pulmonary clearance.
Butler et al. 2011 Australia Pre-post Level 4 N= 11	**Population:** 11 people with SCI (8M 3F); mean(SD) age 45(5); YPI 9.2(4.1); SCI at or above T6 **Treatment:** Bilateral posterolateral surface ES of abdominal expiratory muscles at 50Hz, abdominal binder **Outcome Measures:** Measures of lung function (IC, VC, FVC, FEV_1) gastric pressure (Pga), Pes.	1. Abdominal stimulation increased Pga and Pes during voluntary efforts and during coughing 2. During cough, stimulation significantly increased PEFR by 36(SD 5)%, mean expiratory flow by 80(8)%, expired lung volume by 41(16)% and FEV_1 by 39(12)%. 3. Wearing an abdominal binder increased IC by 17% and VC by 14%. 4. No additional improvement to any respiratory measures during cough with addition of binder to stimulation were found.
Crew et al. 2010 USA Case series Level 4 N = 40	**Population:** 40 patients with tetraplegia; 33 AIS A or AIS B; 14 acute SCI (mean (SD) age 50.3(11.2), YPI 2.3(1.7)) and 26 chronic SCI (58.3(12.9), YPI 22.5(15.1)). **Treatment:** MIE device for outpatient use. **Outcome Measures:** Medical record review (respiratory hospitalization rates/cause).	1. There was a non-significant reduction of respiratory hospitalization rates/year. 2. There was one instance of pulmonary embolus hospitalization post-MIE. 3. Non-smokers averaged 0.14(0.16) respiratory hospitalizations/year, significantly different from smokers (0.41(0.36)). Post-MIE, smokers' respiratory hospitalizations/year decreased significantly to 0.19(0.32).
Nygren-Bonnier et al. 2009 Sweden Pre – post Level 4 N = 25	**Population:** 25 patients with SCI between C4-C8 and ventilatory independent; 20 males and 5 females; mean age 47 (21 – 70) years; ASIA A (n = 12), ASIA B (n = 11), and ASIA C (n = 2); injury level C4 (n = 6), C5 (n = 4), C6 (n = 9), C7 (n = 5), and C8 (n = 1). **Treatment:** The participants performed 10 cycles of glossopharyngeal pistoning (breathing) in a sitting or supine	1. VC, ERV, FRC, RV, TLC, and alveolar ventilation all increased significantly after the training period ($P < 0.05$). 2. Mean GI volume above VC increased a 28% (0.88 ± 0.5 l). 3. PCF changed using GI from 395 ± 83 l min^{-1} to 424 ± 101 l min^{-1}, ($P = 0.057$). 4. No changes were shown in diffusion capacity, MIP or MEP. 5. After training, chest expansion increased significantly during maximal

	position four times a week, for 8 weeks. 5/25 participants could not exceed their VC when trying to perform GI; therefore, they were excluded from analysis. **Outcome Measures:** Spirometry (VC, ERV, FRC [measured with nitrogen washout], RV, and TLC, diffusion capacity, and alveolar ventilation); GI volume; mouth pressure (MIP and MEP); PCF; chest expansion; self-reported adherence; perceived tension in the chest (Borg CR-10 scale); and subjective ability to cough and to clear secretion were measured before and after training period.	inhalation from RV to TLC and also on gulping to TLC_{GI}; 6. Some participants learned the GI technique immediately, whereas others took up to 3 weeks. Training compliance was 87% with a perceived tension on the Borg CR-10 scale during GI of 4 / 10. 7. Participants occasionally reported that during, or shortly after performing GI, temporary symptoms such as dizziness (90%), local paresthesia (35%) and tension in the chest (25%) occurred. Three participants reported episodes of syncope during GI and two reported that they were close to syncope. 8. The participants significantly improved their rating of the two questions concerning cough function and ability to clear secretions. a. Ability to cough: The average reply moved from median 7 (range: 1.5–10; strongly affected) to 3.5 (range: 2–10; P<0.01; moderately affected). b. Ability to clear secretion: The average reply changed from median 7 (range: 0–10; strongly affected) to 4 (range: 1–9; P<0.01; moderately affected).
DiMarco et al 2009 USA Post-test Level 4 N = 9	**Population:** 9 patients with SCI (age range 23-52 yrs). **Treatment:** Lower thoracic SCS at T9, T11, and L1 levels. **Outcome Measures:** Peak airflow and airway pressure generation.	1. Supramaximal SCS resulted in high peak airflow rates (ranging from 5.8 to 8.6L/s) and large airway pressure (ranging from120 to 144 cm H_2O) during stimulation at each electrode lead. 2. Maximum airflow rates and airway pressure were achieved with combined stimulation of any two leads. 3. At TLC, mean(SD) PEFR and airway pressure generation were 8.6(1.8) L/s and 137(30)cm H_2O.
Gollee et al. 2008 UK Pre-post Level 4 N = 4	**Population:** 4 people with tetraplegia (ages 16, 37, 45, and 49, level of injury C4-C6). **Treatment:** Surface FES of abdominal wall muscles. **Outcome Measures:** Spirometry, end-tidal CO_2 ($EtCO_2$).	1. Significant increase in V_T during quiet breathing (range 0.05-0.23 L). 2. Significant increase in CPF (range 0.04 – 0.47 L/s). 3. Respiratory rate during quiet breathing decreased in all participants when stimulated.

		4. V_E increased by 1.05-2.07 L/min. 5. No significant changes in $EtCO_2$.
Kang et al. 2006 Korea Prospective controlled trial Level 2 N = 40	**Population:** 40 patients with traumatic cervical SCI. **Treatment:** Compared four types of coughs: unassisted PCF inspiratory assist cough flow abdominal thrust cough flow inspiratory assist & abdominal thrust cough flow. **Outcome Measures:** Spirometry, MIP, MEP.	1. MIP more so than MEP showed stronger relationships with PEF during cough maneuvers. 2. All three assisted techniques (2, 3 & 4) showed higher PEFRs. The combined assist (4) showed significantly higher values than the inspiratory or abdominal thrust assist.
Estenne et al. 2000 Belgium Pre-post Level 4 N = 16	**Population:** 16 participants: (8 SCI, 8 non-SCI matched for age, sex, height and weight controls), all 8 SCI participants had complete tetraplegia, C4-C7, mean(SD) age SCI: 39(3.1) yrs; controls: 38(1.8) yrs **Treatment:** Magnetic stimulation of abdominal muscles. **Outcome Measures:** Pga.	1. Maximal stimulation increased Pga to 76.0(11.7) in controls and 29.9(3.7) cmH_2O in SCI participants. 2. The cumulative thickness of the four abdominal muscles was 34% smaller in the people with SCI than in control participants and correlated positively with changes in Pga induced by stimulation.
Garstang et al. 2000 USA Pre – post Level 4 N = 18	**Population**: 18 patients with SCI (C1-T3), 88% were C5 or higher. **Methods:** Surveyed preference for: suctioning or maximal in/exsufflation. **Outcome Measures:** Not specified.	1. Maximal in/exsufflation was less irritating, less painful, less tiring, less uncomfortable. All were clinically significant changes (except less tiring). 2. 16 of 18 patients preferred maximal in/exsufflation and one preferred suctioning; 1 patient had no preference. 3. When surveyed, average time from maximal in/exsufflation was 146 days and from suctioning was 253 days.
Linder 1993 USA Prospective controlled trial Level 2 N = 11	**Population:** 11 people with complete SCI (C4 and below), mean(SD) age: group 1 = 38(11.4) years, group 2 = 36.7(7.2) yrs, average time since injury: group 1 = 12.3, group 2= 18years **Treatment:** Group 1: assisted coughing by: 1) manual assist; or 2) FES. Group 2: assisted coughing by a portable abdominal binder incorporating electrodes. **Outcome Measures:** MEP.	1. In group 1, the MEP significantly increased with FES (mean difference in MEP between spontaneous and FES assisted cough was 33.3 cm H_2O). 2. In group 2, the portable FES device increased MEP from 32.3 to 58 cm H_2O, when compared to spontaneous cough.

Discussion

Respiratory complications are a primary cause of morbidity and mortality in people with SCI. Though some studies have examined the effectiveness of secretion removal techniques, there are discrepancies in how standard pulmonary function is measured (Kang et al. 2006). Limited evidence supports the postulate that improving inspiratory muscle strength (Kang et al. 2006) in addition to expiratory muscle force (Estenne et al. 2000) are important to maximize expiratory flows during cough. IMT (Van Houtte et al. 2008), ES of the expiratory muscles (Linder 1993; Estenne et al. 2000; DiMarco et al. 2009, Butler et al. 2011), and MIE (the application of positive pressure to the airway, then shifting to negative pressure to produce an expiratory flow simulating a cough) as an adjunct to manual respiratory kinesitherapy (Pillastrini et al. 2006) are three potential therapies that can maximize the force produced by the inspiratory and expiratory muscles to increase expiratory flows during cough. RCTs examining the effectiveness of airway clearance techniques in people after SCI are lacking. RMT (Van Houtte et al. 2008) and MIE (Crew et al. 2010) have been shown to decrease infections and respiratory hospitalizations per year.

The series of pre–post studies (DiMarco et al. 2019; DiMarco et al. 2020; DiMarco et al. 2021; DiMarco et al. 2022) showed that spinal cord stimulation (SCS) was effective in the increase of peak expiratory airflow, airway pressure generation, and expiratory muscle function, with an associated effect of ease in raising secretions and decrease acute RTI. Moreover, when this group compared the clinical outcomes of wire electrodes (which can be placed using minimally invasive techniques and associated reduction in cost, surgical time and overall risk) and disc electrodes, they showed no differences in the increase of secretions between types of electrodes (DiMarco et al. 2022).

GPB can be used to increase lung volumes and assist secretion clearance in patients with high tetraplegia (Pryor 1999) and in ventilator users, GPB can provide security in case of ventilator failure or for brief periods of ventilator-free breathing (Dail et al. 1956). Nygren-Bonnier et al. (2009) showed that a GPB training for 8 weeks could be adopted by most patients (20/25) and provided an increase in most pulmonary function parameters (VC, ERV, FRC, RV, TLC, and alveolar ventilation), an additional insufflation of 28% of their VC; and an improvement of subjective ability to cough and clear secretions. However, the participants had occasional symptoms during glossopharyngeal insufflation (GI) such as dizziness, increased tightening of the chest, localized numbness, and fainting (syncope). The more recent pre–post study of Nygren-Bonnier et al. (2018), compared the acute effects of GI and showed greater increases in the group with SCI in TLC, VC, mouth airway pressure, HR and in the decrease in MAP, though there were no difference between groups in supine position.

Further study in SCI should examine the effectiveness of hand-held devices that facilitate airway clearance, such as those that apply continuous (Peripep®) or oscillating positive expiratory pressure (Flutter). Of equal concern is to evaluate the comfort and preference of airway clearance techniques that are readily adhered to and performed by people with SCI. Some evidence supports the effectiveness of these positive expiratory pressure devices and other secretion removal techniques such as autogenic drainage in people with cystic fibrosis and other chronic respiratory diseases; however, the evidence to date is somewhat equivocal (Hess 2001; Reid & Chung 2004).

13.1Gap: SCI Evidence on the use of LVR (Lung Volume Recruitment) and Assisted Cough for Secretion Management

- **Source of evidence**: We found one study using LVR for people with SCI (see above Molgat-Seon et al. 2017). However, there is a large body of evidence from other populations with neurological respiratory impairment and cough impairment, predominantly Duchennes Muscular Dystrophy, Amyotrophic Lateral Sclerosis and Multiple Sclerosis.
- There are a variety of LVR techniques possible: using a LVR resuscitation bag, using a MIE machine or using the Ventilator for individuals already using one.
- **Recognizing risk of impaired secretion clearance:** Patients with SCI commonly develop restrictive lung disorders as a result of their decreased respiratory muscle strength, reduced VC, ineffective cough and reduced lung and chest wall compliance. These acute and chronic chest changes place people with SCI at risk for cardiorespiratory complications such as atelectasis, secretion retention and recurrent chest infections. Mechanical in-exsufflation (e.g., cough assist machines), lung volume augmentation techniques (e.g., breath-stacking) and manual assisted cough techniques are recommended as best practice for managing acute and chronic cardiorespiratory conditions in people with SCI. Persons with a PCF of less than 270 L/min are at risk for secretion retention and need manual or mechanical assistance to avoid serious complications or health risks.
- **Management:**
    - **Assisted cough:** this is a manual technique used to increase expiratory pressure. It is used to compensate for the decreased intra-abdominal pressure that can be present with certain levels of SCI. Pressure is applied in the direction of the costal and abdominal areas during expiration. It can be done in lying or sitting PRN depending on need. Appropriate communication and timing are required to ensure that the manual thrust is done just at or prior to expiration. There are some precautions and contraindications mostly related to abdominal trauma, fractures etc.

Figure 9. Manual assisted coughing

- **LVR:** is also called "breathstacking". It is a technique used to compensate for the decrease in inspiratory volume and to achieve maximum insufflation capacity (maximum volume of air that can be held in lungs with glottis closed). To perform this technique a LVR kit is used. It consists of a resuscitation bag and a one-way valve and flex tube with a mouthpiece. Breaths are then "stacked" (taken one after another) to fully inflate the lungs. There may be some tightness or feeling of stretch. An assisted cough can be done at the time of maximum inflation to assist with secretion clearance and increase PCF. Although this is recommended for secretion clearance during times of congestion it is also recommended as a daily treatment to maintain chest mobility and chest hygiene.

Figure 10. Lung Volume Recruitment (LVR) or "Breathstacking" kit

Conclusion

Secretion removal techniques are common practice in people with SCI and yet there is predominantly level 4 evidence to support the use of some airway clearance techniques to facilitate secretion removal in this population.

There is level 2 evidence (from two RCTs: Pillastrini et al. 2006; Jeong & Yoo 2015) in support of MIE coupled with manual chest therapy kinesitherapy techniques.

There is level 4 evidence (from four pre-post studies: DiMarco et al. 2019; DiMarco et al. 2020; DiMarco et al. 2021; DiMarco et al. 2022) that SCS improves expiratory and inspiratory muscle function, peak expiratory airflow, airway pressure generation; with a subsequent increment of ease in raising secretions and descend of acute RTI.

There is level 4 evidence (from one pre–post study: Nygren-Bonnier et al. 2009) that a GPB training period of 8 weeks provides beneficial effects on respiratory parameters (as measured by VC, ERV, FRC, RV, TLC, and alveolar ventilation) and in subjective ability to cough and clear secretions in patients with cervical SCI.

There is no evidence in support of one airway clearance technique over another, and there are no criteria available to indicate when to implement the various airway clearance techniques.

There is a need to determine the most efficient and effective techniques that are comfortable and readily adhered to for people with SCI in order to facilitate airway clearance, improve their QOL, and decrease health care costs.

Key Points

There is limited evidence that suggests that improving inspiratory and expiratory muscle force is important to maximize expiratory flow during cough.

Cough effectiveness can be enhanced by a variety of methods including manual assistance by a caregiver, RMT, GPB, SCS, and/or ES triggered by the person with SCI.

Hand-held expiratory pressure devices may enhance secretion removal in people with SCI.

14 Electrical Stimulation (ES)

14.1 Phrenic Nerve and Diaphragmatic Stimulation

ES options for the restoration of inspiratory muscle function in people with SCI include bilateral phrenic nerve pacing, bilateral diaphragmatic pacing and combined intercostal muscle stimulation with unilateral phrenic pacing (DiMarco et al. 2005a).

Intact phrenic nerves are required for successful stimulation. Phrenic nerve function is generally assessed through phrenic nerve conduction studies and fluoroscopic observation of diaphragmatic movement with PNS. People with injuries at C3, C4 and C5 may have compromised diaphragmatic function, but are unlikely to be candidates for pacing due to inadequate phrenic nerve function.

Bilateral PNS was first reported by Glenn and colleagues in the 1970s. The original surgery involved a thoracotomy and inpatient hospital stay to place the electrodes on the phrenic nerves in the neck or thorax. Potential risks included direct injury to the phrenic nerves during surgery. The original protocols applied intermittent high frequency stimulation to the diaphragms in an alternating pattern, but were revised to a continuous lower frequency stimulation to decrease diaphragmatic fatigue (Glenn et al. 1984; Elefteriades et al. 2002).

In recent years, the laparoscopic placement of intramuscular diaphragmatic electrodes has eliminated the need for more extensive thoracotomy surgery and associated hospital stays. The approach has also decreased the risk of phrenic nerve injury (DiMarco et al. 2005a). The electrodes are placed laparoscopically as a day surgery procedure with optimum placement of the electrodes being mapped to the phrenic nerve motor point (Onders el al. 2004).

Most patients with diaphragmatic pacemakers continue to have tracheostomies and mechanical ventilators as a back-up to their pacemakers. It is important to note that diaphragmatic

pacemakers only improve inspiratory function and do not target expiratory functions such as coughing and clearing secretions. Given the small number of controlled trials and large number of pre-post trials, the full data extraction and scoring are only shown for the controlled trials with a briefer summary of the level 4 evidence.

Table 17. Phrenic Nerve and Diaphragmatic Stimulation – Controlled Trials

Author Year Country Research Design Score Sample Size	Methods	Outcome
Hirschfeld et al. 2008 Germany Cohort Level 2 N = 37	**Population:** 64 participants with SCI who were primarily mechanically ventilated through TOT; 32 were treated with PNS and 32 were treated with MV over 20 years. **Treatment:** MV or PNS. **Outcome Measures:** Incidence of RI.	1. Incidence of RI was equal during 120 days prior to use of final device (1.43 in PNS group and 1.33 in MV group) whereas after PNS, the incidence of RI was 0 compared to 0.14 for MV group. 2. Two vs. 0 returned to work and 9 vs. 2 returned to school on PNS compared to MV group, respectively.

Table 18. Phrenic Nerve and Diaphragmatic Stimulation – Level 4 Evidence

Author	Participants	Intervention	Outcomes	Complications
Wijkstra et al. 2022	33 patients with cervical SCI, with a complete or partial dependency on MV; 24 males and 9 females; mean (SD) age 30.6 (± 20.2) years; incomplete Injury (n = 10) and complete injury (n = 22).	DPS laparoscopically.	1. Usage of DPS increased with increasing time of device use. 2. At 6 months, 19 (73.1%) and 11 (42.3%) patients were using DPS for ≥4 and ≥15 h a day, respectively. Six (23.1%) patients used DPS for 24 h a day, and were completely liberated from MV. 3. After further use and acclimation, the number of patients using DPS for ≥4 and ≥15 per day were 17 (77.3%) and 11	1. Pneumonia was the most common adverse effect and was most commonly seen (63.6%) in patients during the first 3 months post-implant, during a period when they were using MV for time periods ranging from 16 to 24 h/day. 2. Other respiratory events included pneumothorax (n = 3) and atelectasis (n = 2).

Author	Participants	Intervention	Outcomes	Complications
			(50.0%), respectively, and 8 (36.4%) patients were completely liberated from MV use.	
Monden et al. 2022	28, C1-C5 high tetraplegia	DPS implant	1. Median DPS use per day was 15.0 hours 2. 4/28 paced hall-time (median time of 5.5 hours breathing indecently per day). 3. 22/28 still used MV when not using their DPS.	Within 2 weeks of DPS implant: 1. 23/28 no complications. 2. 5/28 complications (broken or misplaced leads, needing extra time to heal from surgery, pneumothorax, pneumonia, and adverse reaction to the pacer [sodium / potassium deficiency]). 3. 7/28 additional surgery for complications or DPS malfunction. After 2 weeks of DPS implant: 1. 21/28 no complications. 2. 4/28 pain and infection at the wire sites. 3. 6/28 pneumonia/aspiration. 4. 5/28 spasticity. 5. 26/28 fewer or no changes in the occurrence of aspiration. 6. 24/28 fewer or no changes in infection/pneumonia compared with before implantation.
Onders et al. 2018	92 patients with traumatic SCI (C1-C6)	DPS	1. 81/92 achieved 4 consecutive hours of pacing. 2. 56/92 utilized DP full time 24 hours a day with no MV. 3. 14/92 used DP >12 hours. 4. 5/92 were not successful in weaning off MV.	1. 31/92 deaths. a. 17/31 exact cause of death known. b. In the group in which DP did not allow weaning, 4 of 5 patients died an average of only 9.9 months from injury. 2. Overall survival, from injury, was a median of 22.2 years (95% confidence interval: 14.0–not reached).

Author	Participants	Intervention	Outcomes	Complications
			5. 24/33 (implanted in the first year) success in being removed from the ventilator 24 hours a day. 6. 22/43 (implanted in second year) success in being able to be off of the ventilator 24 hours a day with DP.	
Nandra et al. 2017	4, high cervical SCI tetraplegia with loss of phrenic nerve function and 100% ventilator dependent	Intercostal nerve transfer in diaphragmatic pacing	1. 1/4 pacing up to 24 h per day. 2. 2/4 trials up to 2 h off ventilator 3. 1/4 trials up to 8 h off ventilator.	1. 2/4 none. 2. 1/4 required replacement of leads at 14 months because of hardware malfunction. 3. 1/4 required repositioning of 1 electrode at 5 months because of displacement of the lead. 4. 0/4 infections or reversal to ventilator dependence.
Verin et al. 2017	4 with cervical SCI, and ASIA A tetraplegia	Unilateral diaphragmatic reinnervation by the inferior laryngeal nerve.	During surgery and immediate post-operative care: 1. ICU LOS ranged from 5 to 8 days. 2. Post-operative diaphragm assessments (day 10 and month 1) did not reveal any change. Follow-up from 6 to 24 months: 1. 3/3 showed no changes in nasoendoscopic findings, no swallowing disorders for food or liquid, no episode of laryngeal aspiration or bronchial	During surgery and immediate post-operative care: 1. 0/4 early troubles with swallowing. 2. 0/4 significant changes in voice. Follow-up from 6 to 24 months: 1. 1/4 death (unexplained cardiac arrest at 6 months). 2. 1/4 moderate severe pulmonary embolism, with no distant consequences. 3. 1/4 severe pneumonia with septicemia and urinary tract infection, with complete resolution.

Author	Participants	Intervention	Outcomes	Complications
			penetration, and no noticeable change in voice. 2. 3/3 showed bilateral response (diaphragm contraction) to cervical magnetic stimulation at 2 years. 3. 0/3 restoration of automatic ventilation at 36 months.	
DiMarco et al. 2014	10 participants with complete SCI (8M, 2F). Users of SCS device for >= 2 years Mean (SD) age: 35.6 (13.4) years Median (SD) DOI: 8.7 (3.5) years	Implanted SCS device	1. Significantly greater Maximum expiratory pressure (MEP) during SCS at 1 year and 4.6 (mean) year follow-up, compared to pre-implant 2. Significantly lower frequency of suctioning / assisted cough (S/AC) and severity of S/AC episodes at 1 year and 4.6 (mean) year follow-up, compared to pre-implant 3. Significantly less difficulty and greater ease in raising sputum at 1 year and 4.6 (mean) year follow-up, compared to pre-implant.	1. Seven of the 10 participants continue to experience mild leg jerks with stimulation, but these are painless and do not interfere with use of the device.
Kaufman et al. 2015	14 patients with SCI ventilated with phrenic nerve lesions; 11M, 3F;	Diaphragmatic pacemaker implantation and bilateral	13 patients showed diaphragm reinnervation; 8 patients achieved >1 h/day ventilator weaning; 2 patients	No intraoperative complications; 1 patient developed bilateral pleural effusions; 3 patients required revision surgery for

Author	Participants	Intervention	Outcomes	Complications
	Median (range) age: 27 (10-66)	nerve transfer	recovered voluntary diaphragm control and spontaneous respiration without pacemaker	replacement ore repositioning of receiver. After final data collection, 1 patient expired due to cardiac arrest, 1 patient stopped pacing.
Hirschfeld et al. 2013	35 (26M, 9F); age at implantation 28 (19) 2–71 yrs	PNS	27 patients (77%) had stable threshold current over an average of 6.3yrs.	Eight of 35 had threshold currents that exceeded 1mA, which might be suggestive of surgical trauma, infection, or reaction to foreign body.
Tedde et al. 2012	5 (3F, 2M) participants with C-SCI; ages 16-40yrs; Level: C2C3 to C4C5	Implantation of a laparoscopic DPS	The diaphragmatic pacemaker placement was successful in all of the patients. After 6 mos, 3 used DPS for 24 hrs, 1 used DPS for up to 6 hrs complemented by MV and 1 discontinued DPS.	Two patients presented with capnothorax during the perioperative period, which resolved without consequences. Diaphragmatic stimulation was discontinued in one patient after onset of uncontrolled neuropathic pain.
Le Pimpec-Barthes et al. 2011	20; 14 males and 6 females, mean age 27.1 years requiring full-time ventilatory support. 18 high cervical spinal injuries above or at C3 level.	Intrathoracic phrenic stimulators.	1. At 36-month follow-up, 18/20 patients had been successfully weaned from the ventilator with a mean weaning time of 6 weeks. 2. All patients who were successfully weaned report an improvement in comfort and QOL.	1. No surgical complications. 2. At 5-year follow-up, 7/20 of participants died (two secondary to pneumonia).
Khong et al. 2010	19 patients (14 with quadriplegia [n = 13] or complete tetraplegia (n = 1))	PNS performed via either a cervical (n = 11) or thoracic approach (n = 6)	1. 11 patients were still actively implanted at the date of study publishment, with total pacing duration ranging from 1 year to 21 years. 2. The average pacing duration for actively pacing patients in whom records were	1. 1/19 experienced malfunction of the diaphragmatic pacemaker 4 years after initial surgery, requiring ventilation at home. 2. 1/19 required lead replacement on the right side due to mechanical failure of implanted components and required full ventilation during sleep for 1 month.

Author	Participants	Intervention	Outcomes	Complications
			available was 13 years. 3. Several of the patients were either lost to follow-up or the records were unobtainable.	3. 1/19 experienced failure of both left-sided and then right-sided receivers due to breast development. 4. Of the patients on whom follow-up information was readily obtained, several complications were noted in most (included recurrent RTI, urinary tract infections, pressure sores, kyphoscoliosis, neurogenic bladder and muscle spasms).
Alshekhlee et al. 2008	26, chronic tetraplegia C1-C4 (25 traumatic, 1 non-traumatic)	DPS	25/26 were able to pace off the ventilator for more than 4 hours per day.	One patient experienced severe muscle cramping and could not achieve conditioning.
DiMarco et al. 2005a	5, ventilator - dependent tetraplegia	Laparascopic placement of intramuscular diaphragm electrodes	4/5 achieved substantial inspired volumes and were maintained without mechanical ventilatory support for prolonged time periods. 1/5 had no response to stimulation	1/5 developed pneumothorax.1/4 developed shoulder pain during maximum stimulation, and another had intermittent aspiration of food during meals.
DiMarco et al. 2005b	4, ventilator - dependent tetraplegia with unilateral phrenic nerve function	Inspiratory intercostal muscle stimulation combined with phrenic nerve (thoracic) stimulation	4/4 achieved inspired volumes such that they could be maintained off MV between 16 and 24 hours a day.	Stimulation of the upper thoracic region was associated with mild flexion of the hand and upper trunk musculature. 1/4 participants developed symptoms of autonomic dysreflexia with stimulation, 1/4 developed shoulder pain, while another developed an infection at the receiver site.
Onders et al. 2004	28 (mapping group) n = 6 tetraplegia implantation group)	Mapping the phrenic nerve motor point via ES, and laparaoscopic DP	The phrenic nerve motor point was found in 23/28 participants. 5/6 had successful implantation, with three completely free	One patient had asymptomatic small pneumothorax, and another had a wound infection.

Author	Participants	Intervention	Outcomes	Complications
			of the ventilator and 2 progressively increasing their time off the ventilator.	
Elefteriades et al. 2002	12, C1/2 - C2 tetraplegia	Bilateral PNS and diaphragm conditioning	Long-term follow up outcomes. 6/12 paced full-time (mean 14.8 years) 1/12 paced full-time for 6.5 years before lapsing to part time 3/12 paced for an average of 1.8 years before stopping 2/12 were deceased: 1 paced for 10 years.	Patients who stopped pacing full-time did so due to inadequate financial or social support, or because they were institutionalized.
Krieger & Krieger 2000	6, C3-C5 tetraplegia	Intercostal to phrenic nerve transfer; PNS	5/6 cases have had longer than 3 months for axonal regeneration. 5/5 regained diaphragmatic motion with phrenic stimulation.	None reported

Discussion

Recent studies show higher success rates with long-term implantation (DiMarco et al. 2014; Hirschfeld et al. 2013); 77% of patients had stable threshold currents for an average of 6.3 yr. Hirschfeld et al. (2008) prospectively compared people receiving PNS and those receiving MV. Although they showed decreased rates of RI and increased social participation in the PNS group, they acknowledged that the MV group is not a comparable group as these participants were not usually candidates for PNS.

The prospective study by Hirschfeld et al. (2008) shows no difference in duration of life between the phrenic nerve paced group and mechanically ventilated group.

Hirschfeld et al. (2008) comment on decreased costs of care, improved quality of speech and higher rates of social participation in the phrenic nerve group. The increased rates of return to work and school may have been influenced by the lower ages seen in the phrenic nerve group. Prospective comparison studies looking at morbidity, mortality, QOL and costs related to phrenic and diaphragmatic pacing are lacking.

Several different devices for phrenic nerve pacing have been developed. Reported benefits to participants include improved sense of smell, mobility, quality of speech, comfort, QOL, and overall sense of well-being (Le Pimpec-Barthes et al. 2011; DiMarco et al. 2005b). Long-term

partial or total independence from MV can be interpreted as a successful intervention with these devices.

Bilateral phrenic nerve pacing and bilateral diaphragmatic pacing can be used successfully for the ventilation of people with SCI (Kaufman et al. 2015; Baer et al. 1990; DiMarco et al. 2005a; Elefteriades et al. 2002; Onders et al. 2004). More recent studies have included larger sample sizes, including the study by Onders et al. (2018) (n = 92); Wijkstra et al. (2022) (n = 33); Monden et al. (2022) (n = 28); and Alshekhlee et al. (2008) (n = 26).

The diaphragm pacing system (DPS) is a successful strategy for managing respiration in patients with high SCI; between 73% and 77% of participants achieved 4-h of independent use of the DPS at 6 and 12 months of follow-up (Wijkstra et al. 2022). The use of a DPS requires a period of acclimation to achieve full effectiveness of the therapy, especially if the patient has been mechanically ventilated for a long period, due to increased levels of diaphragm atrophy and greater dependence on MV (Wijkstra et al. 2022). Some studies recommend early implantation of the DPS (Onders et al. 2018) and a gradually increased and individualized diaphragm conditioning period (Alshekhlee et al. 2008; DiMarco et al. 2005a; Onders et al. 2004; Tedde et al. 2012).

Unilateral phrenic pacing in combination with intercostals stimulation can be used successfully for the ventilation of people with SCI with only one intact phrenic nerve (DiMarco et al. 2005b). Several small studies (Krieger & Krieger 2000; Nandra et al. 2017; Verin et al. 2017) report successful reinnervation of the diaphragm in intercostal to phrenic nerve transfer in patients with SCI. Verin et al. (2017) showed no changes in nasoendoscopic findings, no swallowing disorders for food or liquid, no episode of laryngeal aspiration or bronchial penetration, or no noticeable change in voice were shown at 6 to 24 months of follow-up. However, this procedure was associated with diaphragm reinnervation, even if at 36 months none of the patients could restore their automatic ventilation (Verin et al. 2017). Dimarco et al. (1994) found that intercostal muscle pacing via upper thoracic ventral root stimulation alone has not succeeded in supporting ventilation for prolonged periods. There is at least one case report of the successful off label use of a spinal cord stimulator (rather than a purpose built phrenic nerve stimulator) being used to stimulate the phrenic nerves in people with SCI (Taira & Hori 2007).

Potential complications of phrenic pacing include wires breaking, wires or receivers becoming displaced, devices failing, aspiration of food during inspiration, shoulder or abdominal pain and infections (Baer et al. 1990; DiMarco et al. 2005a, 2005b). With the laparoscopic approach for DP, people may develop pneumothoraces or subcutaneous emphysema (DiMarco et al. 2005a).

Conclusion

There is level 3 evidence (from one case control study: Carter 1993) that suggests a higher survival rate in a phrenic nerve paced group compared to a mechanically ventilated group.

There is level 4 evidence (from 10 pre-post studies and two case series: see Table 18) that PNS can be used as a long-term alternative to MV for people with injuries at C2 or above.

There is level 4 evidence (Tedde et al. 2012; DiMarco et al. 2005a; Onders et al. 2004; Onders et al. 2018; Wijkstra et al. 2022) that diaphragmatic stimulation via laparoscopic placement of electrodes can be used as a long-term alternative to MV for people with high cervical SCI.

There is level 4 evidence (from one pre-post study and two case series: Alshekhlee et al. 2008, Onders et al. 2018; Wijkstra et al. 2022) and level 5 evidence (from one observational study: Monden et al. 2022) that DPS can help patients with cervical SCI to breathe without a mechanical ventilator.

There is level 4 evidence (from one study: DiMarco et al. 2005b) that unilateral phrenic stimulation, in combination with intercostals stimulation, can be used as an alternative to MV for people with a single intact phrenic nerve.

There is level 4 evidence (from one pre – post study: Nandra et al. 2017) that intercostal to phrenic nerve transfer was feasible and successful in reinnervating the diaphragm and limiting ventilator dependence in patients with SCI.

There is level 4 evidence (from one pre – post study: Verin et al. 2017) that the unilateral diaphragmatic reinnervation by the inferior laryngeal nerve is feasible and provides diaphragm reinnervation, but does not restore the automatic ventilation in ventilator-dependent patients with cervical SCI.

There is level 4 evidence (from one study: DiMarco et al. 1994) that intercostal muscle pacing via upper thoracic ventral root stimulation cannot be used as a long-term alternative to MV.

Key Points

There is some evidence that suggests a higher survival rate in phrenic paced participants compared to mechanically ventilated participants.

Phrenic nerve or diaphragmatic stimulation may be used as a long-term alternative to MV for people with injuries at C2 or above.

DPS can help patients with SCI to breathe without a mechanical ventilator.

There is some evidence that restoration of diaphragm innervation through nerve transfer (using intercostal or inferior laryngeal nerve) into the phrenic nerve is feasible and successful in reinnervation of the diaphragm in patients with SCI, but the evidence regarding achieving ventilator independence is still contradictory.

14.2 Abdominal Neuromuscular Electrical Stimulation (NMES)

Abdominal NMES can be used in conjunction with voluntary efforts (depending on the level of SCI) to improve forced expiratory maneuvers including cough.

Table 19. Abdominal Neuromuscular Electrical Stimulation (NMES)

Author Year Country Research Design Score Sample Size	Methods	Outcome
McBain et al. 2015 Australia Pre-post Level 4 N = 7	**Population:** 7 patients with SCI (7M 0F) Mean (SEM) age: 56(4) Mean (SEM) DOI: 18(7.5) years All with motor impairments above C7 **Treatment:** Abdominal muscle ES. **Outcome Measures:** Pga and Pes, PEFR during cough.	1. Significant increase in mean Pga, Pes, PEF during cough and total expiratory volumes from near TLC and expiratory volume below FRC during stimulated cough. 2. Significantly greater increase in Pga, Pes, PEF during cough and total expiratory volumes from near TLC with increasing stimulus intensity. 3. Pga & Pes did not plateau except in one patient at intensity of 400mA. 4. PEF during cough plateaued in all patients at a mean(SD) intensity of 211(29)mA and expiratory volume of 4.0(0.4)L.
McBain et al. 2013 Australia RCT (crossover) PEDro = 5 Level 2 N = 15	**Population:** 15 males with SCI (C4-T5); mean (SD) age: 45(4); DOI: 11.9(4.3) yrs. **Treatment:** All participants trained for 6 weeks, 5 days per week (5 sets of 10 coughs per day). Participants coughed voluntarily at the same time as a train of ES was delivered over the abdominal muscles via posterolaterally positioned electrodes (50Hz, 3s). **Outcome measures:** Pes and Pga expiratory pressures, peak expiratory flow (PEFcough) produced before, during, and after the training.	1. During voluntary coughs, FES cough stimulation improved Pga, Pes, and PEFcough acutely, 20-fold, 4-fold, and 50%, respectively. 2. Six weeks of cough training caused further improvements. It significantly increased Pga (SD) from 37.1(2.0) to 46.5(2.9)cmH_2O, Pes from 35.4(2.7) to 48.1(2.9)cmH_2O, and PEFcough from 3.1(0.1) to 3.6(0.1) L/s. 3. Cough training also improved pressures and flow during voluntary unstimulated coughs.
McLachlan et al. 2013 UK Longitudinal study Level 4 N = 12	**Population:** 12 participants with tetraplegia (11M;1F); median age: 31 yrs (range: 18-73); 7 AIS A, 5 AIS C; median DOI: 5 months (range: 2-94). **Treatment:** 3 weeks of abdominal muscle conditioning using transcutaneous abdominal FES. **Outcome measures:** FVC, FEV_1, PEFR, MEP.	1. Mean (SD) FVC increased by 0.36(0.23) L during training. 2. No significant changes were found in mean FEV_1 and PEF. 3. No significant change was found in the outcome measures during a 1-week pre-training control phase and during a 3-week post-training phase.

Hascakova-Bartova et al. 2008 Belgium Prospective controlled trial Level 2 N = 10	**Population:** 10 participants with SCI, age range 23 – 71 years; 9M 1F, lesion level T10 – C5; 6 with AIS-A, 4 with AIS-B or C. **Treatment:** 4 participants were assigned to abdominal neuromuscular ES for 25 min daily for 8 weeks. 3 participants receive placebo, and 3 had placebo followed by ES. **Outcome Measures:** FVC	1. ES significantly worsened FVC when measured during non-stimulation in the ES group. 2. In the placebo-controlled group there were no differences in FVC. 3. In the placebo-followed by ES group, after ES all participants has worsened FVC.
Spivak et al. 2007 Israel Pre-post Level 4 N = 10	**Population:** 10 male patients aged 22-60 years with tetraplegia. AIS- A n=2; AIS B n=7l; AIS C n=1 **Treatment:** Respiratory tests: 1) without assistance; 2) with manually assisted expiration; 3) FES-assisted expiration activated by a caregiver; 4) manually self-activated FES-assisted expiration; and 5) FES-assisted expiration activated by EMG signals elicited from the patient's own muscle. **Outcome Measures:** PEF, FVC, MVV.	1. With unassisted breathing, PEF, FVC, MVV were 60% lower than that expected in people without SCI. 2. Manual assistance significantly improved the mean PEF by 36.7%, and FVC by 15.4%. MVV improved but was not significant. 3. FES did not significantly change the measurements, however, EMG-activated FES significantly increased PEF and FVC by 15.8 and 18.9% respectively when compared to patient-activated FES.

Discussion

McCaughey et al. (2016) showed that abdominal functional electric stimulation is an effective technique for improving respiratory function in both an acute (as measured by cough peak flow [CPF]) and chronic manner (as measured by FVC, VC, and PEF) in people with SCI. However, low participant numbers and heterogeneity across studies reduced the power of the meta-analysis and the establishment of the clinical efficacy of this technique.

A RCT (McBain et al. 2013) showed that ES delivered over abdominal muscles via posterolaterally positioned electrodes during cough improved abdominal and esophageal pressures as well as the cough expiratory flow rate. With 6 weeks of cough training, these pressures showed even greater improvements. Cough training also improved pressures during unstimulated coughs.

Less promising results have been shown by others (McLachlan et al. 2013; Hascakova-Bartova et al. 2008) who also studied the effect of abdominal NMES on FVC. Smaller sample sizes, different methods, and shorter training periods may in part, explain their conflicting results.

Conclusion

There is level 2 evidence (from one RCT: McBain et al. 2013) that abdominal ES during cough improved cough pressure. After cough training, pressure was improved in unstimulated voluntary cough.

There is level 2 evidence (from one prospective controlled trial: Hascakova-Bartova et al. 2008) that abdominal NMES decreases the FVC.

There is level 4 evidence that (from one pre – post study: Spivak et al. 2007) EMG-activated FES significantly improves both PEF and FVC in patients with tetraplegia, when compared to patient-activated FES.

15 Summary

Difficulty clearing mucus, pulmonary embolism, reduced lung capacity, respiratory failure or pneumonia are the main respiratory complications which can occur after a SCI and continue to be one of the leading causes of morbidity and mortality in this population, especially among cervical and higher thoracic injuries. Many risk factors for respiratory problems include completeness of the injury, higher level of injury, or more severe injury, among others. The present review has shown the evidence regarding different therapies and programs for the treatment of respiratory problems in patients with SCI, showing in general a lack of high-quality studies in form of RCTs, while the majority are retrospective or pre-post (without control group) studies.

Regarding the pharmacological options, there is some evidence that different types of medications (such bronchodilators, anabolic agents, or anxiolytics) could have beneficial effects in pulmonary function in patients with SCI. Despite this, there is a need for more quality of evidence as only one study was a high level of evidence (RCT) in this area.

Exercise training of the upper and lower limbs and respiratory exercise are the fields with the largest and the best evidence in this area. While both exercise training regimens have shown beneficial effects in functionality, respiratory function, and respiratory muscle strength of patients with SCI; the ideal training protocols and dosage remain unclear because there is abundant heterogenicity among studies.

Assistive devices and other treatments like abdominal binders, chest wall vibration and immersion seem to improve respiratory function, but more and high-quality studies are needed to provide more robust conclusion and determine the long-term effects in patients with SCI.

Sleep disordered breathing, commonly known as sleep apnea appears to have a higher prevalence in people after SCI, but despite this high prevalence, there are few studies in this area. Only CPAP therapy has proven beneficial clinical effects to treat SDB in people with SCI, while other treatments with medications could not show clinical effects until this date.

ES interventions for the restoration of inspiratory muscle function in people with SCI include bilateral phrenic nerve pacing, bilateral diaphragmatic pacing and combined intercostal muscle stimulation with unilateral phrenic pacing (DiMarco 2005). From the study by Glenn and colleagues in the 1970s, the scientific evidence has been increased. Despite a large number of studies in the area, and the beneficial effects of phrenic nerve and diaphragmatic stimulation as an alternative to MV, there is still a need for more high-quality studies as the majority of them are pre-post studies or case series.

People with SCI are at risk for secretion retention because of an increased prevalence of pneumonia compounded by lower expiratory flows during cough. Secretion removal techniques are common practice in this population and yet there is predominantly only level 4 evidence to support the use of some airway clearance techniques to facilitate secretion removal in patients with SCI, but until this date, there is no evidence of one airway clearance technique over another, and in the same way, there are no criteria available to indicate when to implement the various airway clearance techniques.

The approach to ventilator weaning in SCI remains an important and somewhat neglected issue. There is a distinct lack of controlled trials in respiratory medicine; again, research in this area primarily consists of retrospective reviews and small case series. There is some evidence of different ventilator and weaning protocols are beneficial in the improvement of respiratory parameters, successful weaning, and successful switch to non-invasive ventilation, but prospective studies on mechanical and weaning protocols are required to determine the best way to assess, treat and wean people requiring MV following SCI.

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Abbreviations

AB	abdominal binding
ACZ	acetazolamide
APCF	assisted peak cough flow
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPF	cough peak flow
DP	diaphragm pacing
DPS	diaphragm pacing system
EMT	expiratory muscle training
ERV	expiratory reserve volume
ES	electrical stimulation
ES-LCE	electrical stimulation induced leg cycle ergometry
fb	frequency of breathing
FES	functional electrical stimulation
FESRT	functional electrical stimulation row training
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
FVC	forced vital capacity
FMS	functional magnetic stimulation
GI	glossopharyngeal insufflation
GPB	glossopharyngeal breathing
HFPV	high frequency percussion ventilation
HR	heart rate
HRQOL	health-related quality of life
HVtV	high tidal volume ventilation
LOS	length of stay

IC	inspiratory capacity
ICU	intensive care unit
IH	isocapnic hyperpnoea
IMT	inspiratory muscle training
IMV	intermittent mandatory ventilation
IRV	inspiratory reserve volume
MEP (or PE_{max})	maximal expiratory pressure
MIE	mechanical insufflation-exsufflation
MIP (or PI_{max})	maximal inspiratory pressure
MV	mechanical ventilation
MVV	maximal voluntary ventilation
NIV (or NIMV)	non-invasive ventilation / no-invasive mechanical ventilation
NIV	non-invasive (mechanical) ventilation
NMES	neuromuscular electrical stimulation
OLT	overground locomotor training
OSA	obstructive sleep apnea
OUES	oxygen uptake efficiency slope
PAP	positive airway pressure
Pes	esophageal pressure
$PaCO_2$	partial pressure of arterial carbon dioxide
PaO_2	partial pressure of arterial oxygen
PCF	peak cough flow
PEF (or PEAF)	peak expiratory flow / peak expiratory air flow
PEFR	peak expiratory flow rate
$P_{ET}CO_2$	end-tidal partial pressure of CO_2
Pga	gastric pressure
PIF	peak inspiratory flow
PNS	phrenic nerve stimulation
PSG	polysomnography
PVFB	progressive ventilator free breathing
QOL	quality of life
REM	rapid eye movement
RER	respiratory exchange ratio
RI	respiratory infection

RMT	respiratory muscle training
RPE	rate of perceived exertion
RTI	respiratory tract infections
RV	residual volume
SCI	spinal cord injury
SCS	spinal cord stimulation
SCU	spinal cord unit
sEMG	surface EMG
SGRQ	St. George's Respiratory Questionnaire
SIP	maximal sustainable mouth pressure
SDB	sleep-disordered breathing
TLC	total lung capacity
TOT	tracheostomy
TV (or V_T)	tidal volume
UPCF	unassisted peak cough flow
UNDW	ultrasonically nebulized distilled water
VC	vital capacity
VCO_2	CO_2 production
V_E	minute ventilation
VO_2	O_2 consumption