Traumatic Spinal Cord Injury

Pulmonary Physiologic Principles and Management

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KEYWORDS

• Pulmonary function • Spinal cord injury • Respiratory muscle strength
• Restrictive airway dysfunction • Airway dynamics • Respiratory symptoms • Sleep apnea

KEY POINTS

- Respiratory complications, principally pneumonia, are the primary cause for premature mortality among individuals who have suffered traumatic spinal cord injury, both during the early acute post-injury period and thereafter.
- Due to paralysis of respiratory muscles, traumatic injury to the cervical and upper thoracic spinal cord is associated with restrictive pulmonary dysfunction and respiratory muscle weakness, with greater compromise of expiratory as compared with inspiratory muscle function.
- A significant number of persons with cervical spinal cord injury manifest obstructive physiology characterized by reduction in baseline airway caliber, bronchodilator responsiveness, and nonspecific airway hyperreactivity, although the clinical significance of these findings are unclear.
- Chest physiotherapeutic techniques appear to be effective early adjuncts to prevent atelectasis and promote respiratory clearance during weaning attempts and to help prevent respiratory complications, such as pneumonia, among subjects with high cervical spinal cord injury.
- The prevalence of sleep-disordered breathing among subjects with tetraplegia far exceeds that witnessed in the general population, and implies a unique underlying physiology among these individuals.

INTRODUCTION

Traumatic injury to the cervical and upper thoracic spinal cord is associated with variable degrees of pulmonary dysfunction and disability dependent on the level and completeness of injury. The purpose of this article was to detail the pulmonary function and mechanisms of pulmonary physiologic impairment associated with traumatic spinal cord injury (SCI), and interventions to prevent pulmonary complications associated with attendant decreases in respiratory muscle strength and impaired cough. We

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examine temporal changes in pulmonary function following traumatic SCI and focus on the physiologic principles that govern and affect the ability to breathe spontaneously without ventilatory support. Various interventions discussed include chest physiotherapy, pharmacologic and nonpharmacologic techniques to improve respiratory muscle strength, and electrical pacing techniques. Sleep-disordered breathing also is discussed because of its high prevalence in this population, including current thoughts regarding pathophysiology and management. This review does not address spinal shock, the acute care of the spinal cord–injured patient (including ventilator or tracheostomy management), pulmonary embolism, or management of respiratory complications. With regard to diaphragmatic pacing, the reader is directed to Anthony F. DiMarcos' article, "Diaphragm Pacing," in this issue.

EPIDEMIOLOGY

Significant and lifelong neurologic deficits are all too often the dramatic consequence of traumatic SCI. According to 2017 estimates compiled by the National Spinal Cord Injury Data Center, the annual incidence of traumatic SCI in the United States is approximately 54 cases per 1 million people, or 17,500 new cases per year, and affects approximately 285,000 persons (range 245,000–345,000).[1] Compared with the 1970s, men still comprise approximately 80% of victims of SCI, although the average age at injury has increased from 28.7 years to 42.2 years, a consequence of our aging population and an increase in injuries resulting from falls among older individuals.[2] There has been a corresponding decrease in the percentage of SCIs resulting from vehicular crashes (47% to 38%), although this remains the most common etiology, followed by falls (31%), acts of violence (14%), sports-related injuries (9%), medical/surgical complications (5%), and others (4%).[1,2] Notwithstanding the attendant emotional and physical challenges of SCI, the socioeconomic impact across a lifetime is substantial; according to the National SCI Statistical Center, the estimated lifetime medical cost for an individual injured at age 25 with low tetraplegia is approximately $3.5 million.[1]

The past 40 years have witnessed a substantial improvement in the acute management and short-term 2-year survival in persons with SCI, although the mortality risk remains high during this period, ranging from 3.1% to 21.0%.[3–10] Pulmonary complications pose the greatest risk during the first 2 years postinjury, and include pneumonia, pulmonary edema, respiratory failure, and thromboembolism.[11,12] Despite improved early survival and shorter initial hospital lengths of stay, according to a recent study of data from the National Spinal Cord Injury Model System, the life expectancy for those surviving beyond 2 years postinjury compared with an age-matched noninjured population has declined slightly over the past 30 years, and overall long-term survival for persons with SCI remains significantly less than that of the general population regardless of injury level.[1,13] Historical data also identify a shift in the principal cause of mortality during the chronic phase of SCI; mortality related to urosepsis and renal failure has now been supplanted by sepsis and pulmonary complications, particularly pneumonia.[1,14,15] Thus, pulmonary complications are now a primary cause for morbidity and mortality in the SCI population, regardless of time postinjury.

OVERVIEW OF RESPIRATORY MUSCLE FUNCTION

The principal muscle of inspiration is the diaphragm innervated by the phrenic nerve arising from cervical nerve roots C3 to C5. Dome-shaped, the diaphragm consists of a central tendon and skeletal muscle fibers that insert laterally along the inner surface of the lower 6 ribs and anteromedially along the costal cartilages. The region of diaphragm that closely abuts the lower ribs at functional residual capacity defines the zone of apposition which normally constitutes 30% of total rib cage surface area.[16] With inspiration and muscle shortening, the diaphragm descends and the zone of apposition decreases, thereby increasing the thoracic cavity, displacing abdominal contents caudally, and elevating the lower rib cage.[17] The external intercostal muscles and parasternal portion of the internal intercostals supplied by corresponding thoracic spinal nerves have a synergistic action with the diaphragm during inspiration, serving to elevate the 2nd through 12th ribs.[18,19] Accessory muscles of inspiration, including the sternocleidomastoid (cranial nerve [CN] XI), scalene (C2–C7), and upper trapezius (CN XI) muscles, function to elevate the upper ribs and sternum.[16]

Generally, during quiet breathing, expiration is a passive process, although recruitment of expiratory muscles is essential for force generation during active processes, such a cough or exercise. The principal muscles of expiration are the internal intercostals and the abdominal

muscles. The interosseous internal intercostals are innervated by corresponding thoracic nerves, and their major function is to lower the rib cage (from the 2nd to the 12th ribs). The abdominal muscles involved in active expiration include the rectus abdominis (T5 to L1), and the external and internal oblique muscles (lower 6 intercostal nerves, subcostal nerve), which compress both rib cage and abdomen. Accessory muscles include the clavicular portion of the pectoralis major (C5–C7) and latissimus dorsi (C6–C8).[16]

Optimal function of the diagram is contingent on intact intercostal and abdominal muscle function. In patients with cervical or thoracic SCI, paralysis of intercostal and abdominal musculature impairs diaphragm performance. The tethering effect of the inspiratory intercostal muscles is no longer present in SCI. Therefore, when the diaphragm contracts and lowers pleural pressure, the intercostals can no longer counterbalance the deflationary effects of negative intrapleural pressure on the upper rib cage. Consequently, there is paradoxic inward motion of the upper rib cage during inspiration. In addition, abdominal muscle paralysis increases abdominal compliance, resulting in greater diaphragm shortening for a given tidal volume. The combination of reduced abdominal compliance and paradoxic inward motion of the upper rib cage results in a decrease in diaphragmatic efficiency (less volume inhaled for a given amount of diaphragmatic work), and an increased oxygen cost of breathing.[20–23]

A schematic showing levels of innervation of the inspiratory and expiratory muscles is shown in Fig. 1.

ASSESSMENT OF MOTOR AND SENSORY IMPAIRMENT FOLLOWING SPINAL CORD INJURY

The American Spinal Injury Impairment Scale (AIS) is used to classify the extent of motor and sensory impairment following SCI.[24] Tetraplegia refers to impairment or loss of motor and/or sensory function in the cervical segments (C1–C8), whereas paraplegia refers to impairment or loss of motor and/or sensory function involving the thoracic (T1–T12), lumbar (L1–L5), or sacral segments (S1–S5) of the spinal cord. Motor complete injuries are characterized by complete absence of motor functional preservation below the neurologic level and either a corresponding absence (AIS A) or preservation of sensory function (AIS B). Motor incomplete lesions have variable degrees of residual motor function (AIS C and AIS D) (Table 1). The degree of ventilatory muscle impairment is

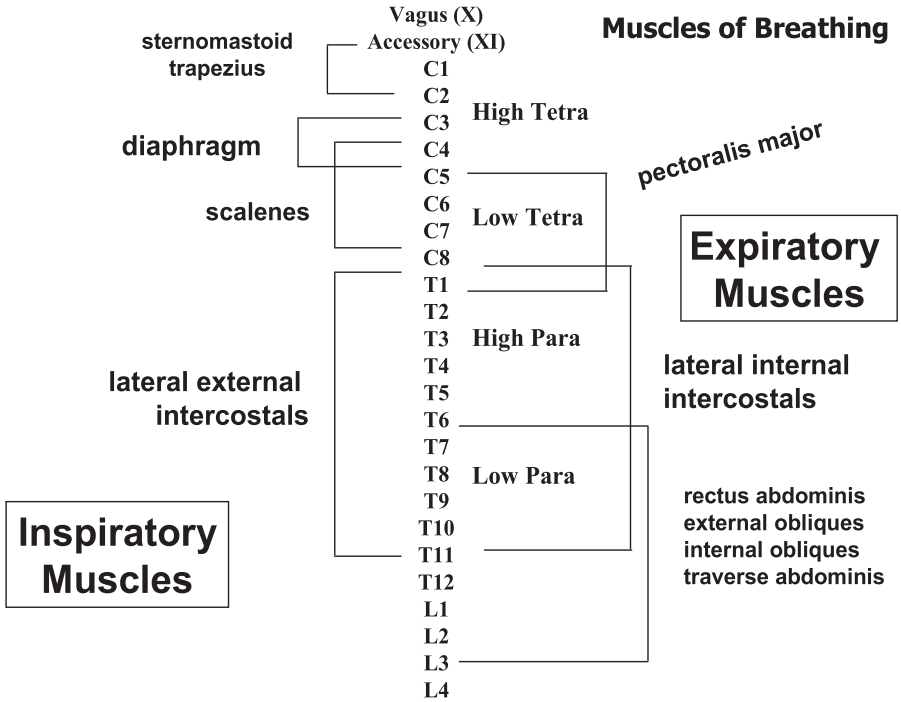

Fig. 1. Respiratory muscles and SCI. (*From* Schilero GJ, Spungen AM, Bauman WA, et al. Pulmonary function and spinal cord injury. Respir Physiol Neurobiol 2009;166(3):130; with permission.)

Table 1
American Spinal Injury Association impairment scale (AIS)

A	Complete cord injury. No motor or sensory function is preserved in the sacral segments S4–5.
B	Sensory incomplete. Sensory but not motor function is preserved below the neurologic level and includes the sacral segments (light touch or pin prick at S4–5 or deep anal pressure) AND no motor function is preserved more than 3 levels below the motor level on either side of the body.
C	Motor incomplete. Motor function is preserved below the neurologic level and more than half of key muscle functions below the neurologic level of injury have a muscle grade <3 (Grades 0–2).
D	Motor incomplete. Motor function is preserved below the neurologic level and at least half (half or more) of key muscle functions below the neurologic level of injury have a muscle grade ≥3.
E	Normal. Sensation and motor function are graded as normal in all segments and the patient had prior deficits.

Muscle function is graded using the International Standards for Neurologic Classification of Spinal Cord Injury. For an individual to receive a grade of C or D (ie, motor incomplete status), he or she must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than 3 levels below the motor level for that side of the body. Patients without an initial spinal cord injury do not receive an AIS grade.

From American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2013; Atlanta, GA. Reprinted 2013. Used with permission. Copyright © 2013 American Spinal Injury Association. American Spinal Injury Association (ASIA) impairment scale (AIS) remained unchanged in the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). © 2011 American Spinal Injury Association. Reprinted with permission.

contingent on the level and completeness of injury, with greater compromise associated with higher cord and complete motor injuries, and is the principal factor underlying pulmonary dysfunction and the attendant risk of respiratory complications. It is useful conceptually to consider the degree of impairment of respiratory function in terms of residual function of the inspiratory muscles, in particular the diaphragm, and that of the expiratory muscles. Residual diaphragmatic function is essential to avert pump failure and to spontaneously breathe without ventilatory support, whereas expiratory muscle function is essential for maintenance of cough strength and effectiveness to reduce the propensity for atelectasis and pneumonia.

Key injury levels as they pertain to the degree of physiologic impairment and recovery are as follows.

Injury Level C1–C3

Complete injury is associated with near-complete absence of function of the muscles of inspiration, principally the diaphragm (C3–C5) and external intercostals (T1–T12), resulting in respiratory pump failure. The muscles of expiration, including the internal intercostals and abdominal muscles, are also nonfunctional. Survival is therefore contingent on the immediate institution of ventilatory support. These patients will most likely be full-time ventilator-dependent, although techniques such as glossopharyngeal or "frog" breathing might facilitate brief ventilator-free periods, and certain individuals might be candidates for diaphragmatic pacing.[25] The indications for diaphragmatic pacing are discussed separately (see section on "Methods to Improve Respiratory Muscle Strength and Pulmonary Function").

Injury Level C3–C5

Mechanical ventilation is frequently required in the first few days to weeks after injury due to respiratory muscle weakness or as a consequence of atelectasis or pneumonia.[3] Variable degrees of residual diaphragmatic and accessory inspiratory muscle function are preserved at the expense of reduced lung volumes and diminished pulmonary reserve. Patients often achieve periods of unassisted ventilation or are supported through nocturnal ventilation, and many with time graduate completely from mechanical ventilatory support.[25] Gradual improvement in respiratory muscle function is noted within the first several weeks to months following injury (see section on "Temporal Changes in Pulmonary Function following Traumatic SCI"), during which time weaning from mechanical ventilation is often realized. Expiratory muscle function and cough effectiveness in motor complete injury will be significantly impaired due to paralysis of expiratory muscles.

Injury Level C6–C8

Complete injury at levels C6 through C8 of the spinal cord is associated with intact innervation to the diaphragm and to accessory neck muscles compatible with independent breathing, although the facilitative effects of intact intercostal and

abdominal muscles on diaphragmatic function are not present. Expiratory muscle function, due to paralysis primarily of the internal intercostals and abdominal muscles, remains significantly impaired. Forced expiration and the ability to generate effective cough in these individuals lies with residual innervation of accessory muscles, principally the clavicular portion of the pectoralis major (C5–C7) and possibly to the latissimus dorsi (C6–C8).[26–28] Thus, these individuals remain vulnerable to respiratory failure as a consequence of increased ventilatory loads as might occur in association with pneumonia or retained secretions.[22]

Failure of individuals with cervical SCI to wean off mechanical ventilatory support may be a consequence of accompanying bulbar weakness stemming from injury to lower cranial nerves. The resultant weakness in pharyngeal and palatal muscles leads to recurrent aspiration and impaired airway protection dictating the need for long-term tracheostomy to facilitate airway clearance. Those persons with intact bulbar function but still requiring ventilatory support alternatively have a better chance of graduating to partial or complete noninvasive ventilation by using techniques such as glossopharyngeal breathing coupled with manually assisted cough ("quad cough") and other forms of chest physiotherapy, and be potentially good candidates for diaphragmatic pacing.[29,30]

Injury Level T1–T12

Thoracic-level SCI is associated with preserved diaphragmatic function notwithstanding some loss of intercostal muscle strength and the stabilizing effects of intact abdominal musculature. The major concern of thoracic-level SCI is the impact on residual expiratory muscle function and cough strength. Cough effectiveness improves as the level of thoracic injury decreases. This is a consequence of progressively greater preservation of expiratory intercostal and abdominal muscle function.

CHEST PHYSIOTHERAPY

Chest physiotherapeutic techniques may prove especially beneficial following acute injury and during the weaning process to promote lung expansion and augment secretion clearance, and also may play a role among those with chronic SCI in association with acute chest infection or as clinically indicated.[3,31] These techniques include manually assisted cough ("quad cough"), mechanical insufflation-exsufflation, suction catheters, therapeutic bronchoscopy, and conventional deep breathing exercises accompanied by frequent changes in body position and postural drainage.[32–35]

The manually assisted or "quad cough" is performed by situating the subject in a supine or slightly upright posture while being straddled by a therapist whose hands are placed under the left and right costal margins. The subject then inhales to total lung capacity, and the therapist applies vigorous pressure to the abdomen timed to coincide with cough efforts. Contraindications include the presence of an abdominal aortic aneurysm or prosthesis, or an inferior vena cava filter.

The mechanical insufflation-exsufflation device consists of insufflation of the lungs with positive pressure, followed by application of negative-pressure that creates a peak and sustained high flow enough to provide adequate shear and velocity to loosen and remove secretions toward the mouth for suctioning or expectoration.[34] The device can deliver in-exsufflation via a mask or a tracheostomy tube, and peak expiratory flows of 6 to 11 L/s can be achieved. Potential, albeit rare, complications include abdominal distention, aggravation of gastroesophageal reflux, hemoptysis, chest and abdominal discomfort, acute cardiovascular effects, and pneumothorax. The device can be used as frequently as every 5 minutes.[33]

Bronchoscopy, as compared with use of suction catheters, allows for direct visualization of the airway and is perhaps the most effective method of secretion clearance. Performance of quad coughs during the bronchoscopic procedure might enhance secretion clearance by mobilizing secretions not otherwise bronchoscopically visible.[33]

TEMPORAL CHANGES IN PULMONARY FUNCTION FOLLOWING TRAUMATIC SPINAL CORD INJURY

The period immediately following traumatic SCI, referred to as spinal shock, is characterized by flaccid paralysis and areflexia below the level of injury.[36] Following cervical SCI, vital capacity and expiratory flows are generally at their lowest, and values of forced vital capacity less than 25% of predicted identify those individuals likely to develop respiratory failure requiring ventilatory support. Significant increases in vital capacity occur within 5 weeks of injury, with approximate doubling of vital capacity within 3 months.[37] Continued improvement in pulmonary function is noted during the remainder of the first year following cervical SCI, during which time pulmonary function parameters, including vital capacity (VC), inspiratory capacity (IC), total lung capacity (TLC), and inspiratory and expiratory flow rates

increase, whereas functional residual capacity (FRC) decreases.[33,38–40] Early improvements in pulmonary function have been attributed to functional decline in the level of SCI coincident with resolution of inflammation and edema above the injury level,[38] and subsequently to improvement in diaphragm function,[33,41–44] in the performance of accessory neck muscles,[45] to the change from flaccid to spastic paralysis,[46] and to increased rib cage stability.[38,43]

ASSESSMENT OF PULMONARY FUNCTION AMONG SUBJECTS WITH CHRONIC SPINAL CORD INJURY

Testing Considerations

Precise measurement of height used to calculate predicted pulmonary function values is problematic among persons with SCI, most of whom cannot stand. Because recalled height may not be accurate, and arm span measurements appear even less reliable, it is recommended that supine length be measured for use in calculating predicted values for pulmonary function.[47] The use of modified ATS/ERS standards for the performance of spirometry also might be necessary for the subset of patients with SCI who are unable to meet acceptable standards due to excessive back-extrapolated volume and/or expiratory efforts lasting less than 6 seconds. Although most subjects with SCI are able to perform spirometry in accordance with acceptable standards for the able-bodied,[48–50] the minority who cannot are generally those with neurologically complete cervical cord injury and lower baseline levels of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). Modification of ATS/ERS standards to permit excessive back-extrapolated volume and expiratory efforts of less than 6 seconds duration allows for 88% of subjects with chronic SCI to provide acceptable and reproducible spirometric efforts.[49]

For measurement of maximal inspiratory and expiratory pressures (MIP and MEP, respectively), a flange-style mouthpiece is generally used. However, in a study of 50 subjects with tetraplegia, MEP values obtained using a tube-style mouthpiece were significantly greater than those obtained by use of an intraoral flange-style mouthpiece due to perioral air leaks around the latter device.[51]

Restrictive Dysfunction

Neuromuscular weakness in persons with chronic tetraplegia and high paraplegia is classically associated with spirometric and lung volume measurements demonstrating restrictive ventilatory defects highlighted by reduction in VC, peak expiratory flow, TLC, expiratory reserve volume (ERV) and IC, as well as an increase in residual volume (RV) and little change in FRC.[40,52–61] Following acute injury, VC was shown to correlate well with other spirometric and lung volume parameters, indicating that during the acute period, VC is a good surrogate of overall ventilatory function.[60] The higher the level of injury, the greater the reduction in pulmonary function parameters (**Fig. 2**),[58] with incomplete injury mitigating FVC loss in tetraplegia.[57,58] Three large cross-sectional studies have assessed spirometry in patients with chronic SCI.[52,62,63] Adjusting for neurologic level and completeness of SCI, Jain and colleagues[62] noted that lower FEV1 values were significantly related to older age, more years since injury, greater lifetime cigarette smoking in pack-years, previous chest injury or operation, a history of clinician-diagnosed asthma, self-report of wheeze, and a lower MIP. A lower FEV1/FVC ratio was associated with older age, greater lifetime cigarette smoking in pack-years, previous chest injury or operation, self-report of wheeze, and greater body mass index (BMI).[62] Similarly, in the study by Almenoff and colleagues,[52] smoking was associated with reduction in FEV1/FVC in patients with tetraplegia and paraplegia, whereas in the study by Linn and colleagues,[63] a consistent effect of smoking was not observed, although reduction in FEV1 was associated with a greater number of years since injury. In addition to level and completeness of injury, determinants of full lung volumes (TLC, FRC, RV, and ERV) included decrease in these parameters with increasing BMI and longer time since injury, increase in FRC and RV with total pack-years of smoking, and increase in RV associated with physician-diagnosed chronic obstructive pulmonary disease.[64]

In a cross-sectional analysis including 455 subjects from 2 large outpatient populations, regression analysis was used to determine % predicted FVC in motor complete SCI; the FVC fell below 80% of predicted, indicating a threshold level for restrictive dysfunction at the T4 injury level and above[58] (see **Fig. 2**). For individuals with C4-C5 motor complete SCI, this model predicts an FVC of 45% to 52% of predicted, very similar to the adjusted FVC value of 55% reported by Jain and colleagues,[62] thus identifying moderate to severe restrictive dysfunction associated with high cervical cord injury.

Airway Dynamics (Obstructive Physiology and Airway Hyperreactivity)

The weight of evidence from numerous studies assessing changes in spirometric indices and

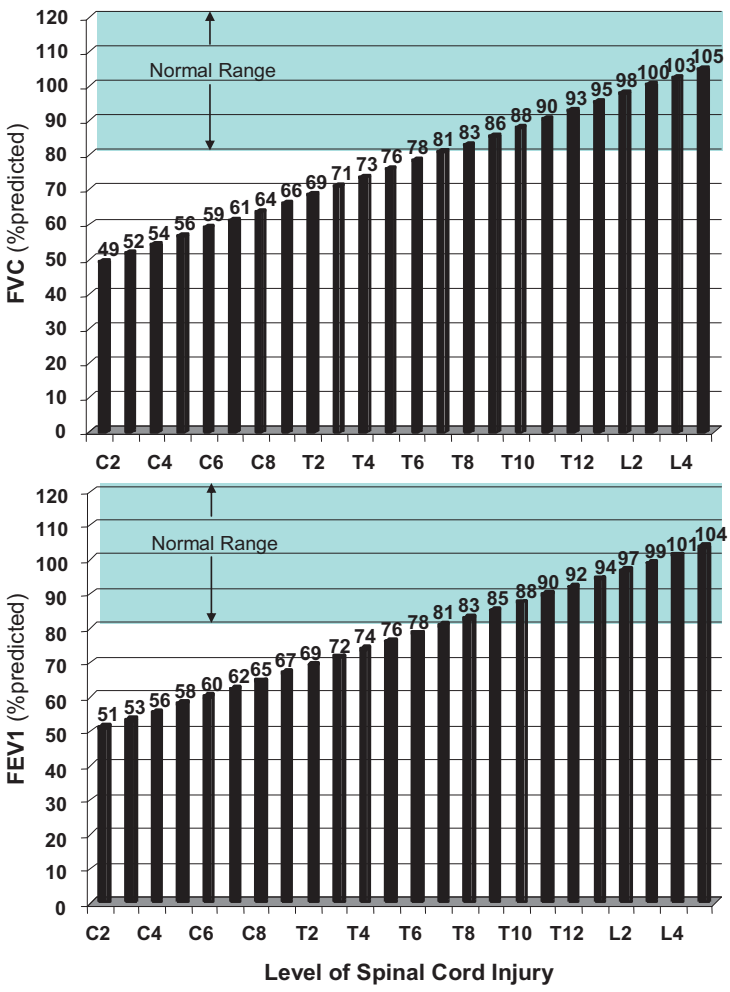

Fig. 2. Level of injury and pulmonary function abnormality. (*Adapted from* Linn WS, Spungen AM, Gong H Jr, et al. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. Spinal Cord 2001;39(5):263–8; with permission.)

specific airway conductance is that subjects with chronic stable tetraplegia have reduced baseline airway caliber and that many exhibit bronchodilator responsiveness following inhalation of either an inhaled beta-2 adrenergic agonist or anticholinergic agent (ipratropium bromide) (**Table 2**), and that these findings are unique to cervical SCI and not evident in lower-level paraplegia (T7 and below).[52,65–70] A recent comparison study demonstrated that the bronchodilator effect of ipratropium bromide was greater than that of the beta-2 agonist albuterol, thereby suggesting by the specific action of anticholinergic agents that heightened cholinergic airway tone exists in tetraplegia.[65] The cumulative findings support the hypothesis that reduced airway caliber and bronchodilator responsiveness in tetraplegia is due to interruption of sympathetic innervation to the lung arising from the upper 6 thoracic nerve roots, thereby resulting in unopposed parasympathetic innervation to airways carried by vagal nerve fibers. Although controversial, and in contrast to earlier studies, the presence of functional sympathetic innervation of human airways is supported by histochemical and ultrastructural studies demonstrating sympathetic fibers reaching the level of secondary bronchi and terminal bronchioles,[71,72] and from studies of dorsal sympathectomy for essential hyperhydrosis that revealed reduction in expiratory flows 6 months following surgery compared with values before surgery.[73–75] Despite these observations, the clinical role of bronchodilators in the management of patients with SCI is unclear, although they are often used empirically in a variety of settings.

Individuals with tetraplegia, but not those with low paraplegia, demonstrate airway hyperreactivity (AHR) in response to methacholine, histamine, and ultrasonically nebulized distilled water.[76–79] Responders to histamine demonstrated reduction in surrogate spirometric indices of airway size and airway size relative to lung size.[80] Similar to the

Table 2
Response to ipratropium bromide in spinal cord injury

Pulmonary Function Parameter	Tetraplegia n = 6		Paraplegia n = 6	
	Mean ± SD	% Change	Mean ± SD	% Change
FEV1, L	2.11 ± 0.57	(12 ± 6)[a]	3.24 ± 0.64	(2 ± 3)
FEV1/FVC ratio	75 ± 4	(5 ± 7)	82 ± 7	(0 ± 2)
ERV, L	0.63 ± 0.56	(57 ± 63)[a]	1.09 ± 0.45	(−7 ± 30)
FRC, L	2.67 ± 1.02	(0 ± 10)	3.16 ± 0.58	(−5 ± 4)[a]
sGaw, $cmH_2O^{-1}s^{-1}$	0.13 ± 0.05	(135 ± 47)[a]	0.26 ± 0.02	(19 ± 7)[a]

Values are mean ± SD for prebronchodilator measurements. Numbers in parentheses represent percent change after administration of ipratropium bromide.

Abbreviations: ERV, Expiratory reserve volume; FEV1/FVC, The ratio of the FEV1 to the forced vital capacity; FEV1, Forced expired volume in 1 second; FRC, functional residual capacity; sGaw, specific airway conductance.

[a] $P<.05$ for percent change from baseline value.

Adapted from Schilero GJ, Spungen AM, Bauman WA, et al. Pulmonary function and spinal cord injury. Respir Physiol Neurobiol 2009;166(3):133; with permission.

bronchodilator studies, one explanation for these findings would be preexisting airway narrowing, in that findings of a further small reduction in airway caliber induced by a bronchoconstrictive agent would produce a large increase in resistance, because airway resistance is inversely proportional to the fourth power of the radius.[81] Support came from further studies demonstrating the ability of: (1) pretreatment with ipratropium bromide to attenuate hyperresponsiveness to ultrasonically nebulized distilled water; (2) pretreatment with baclofen and oxybutynin chloride, both with anticholinergic properties, to inhibit methacholine hyperresponsiveness; and (3) pretreatment with metaproterenol to attenuate methacholine and histamine-induced hyperresponsiveness.[76,79,82,83] Other factors in addition to reduced baseline airway caliber, however, might be needed to explain histamine-induced AHR in subjects with tetraplegia, because neither pretreatment with ipratropium bromide nor administration of baclofen or oxybutynin chloride attenuated responsiveness to histamine.[77,83,84]

Like bronchodilator responsiveness, the clinical implications of AHR among subjects with chronic tetraplegia is unknown, although a recent Canada-wide survey of chronic respiratory disease found that after adjusting for age, sex, and smoking status, SCI was associated with significantly increased odds of asthma and chronic obstructive pulmonary disease.[85]

Effects of Body Position

In contrast to able-bodied individuals, FVC and FEV1 are significantly higher supine as compared with a sitting position.[86–89] The increase in VC when recumbent has been attributed to a reduction in RV due to the effects of gravity on abdominal contents.[89] Greater elevation of the diaphragm in the supine position among those with tetraplegia results in greater downward excursion during contraction because muscle fibers are operating at a more favorable portion of their length-tension curve.[54,87,89] The concept of a more favorable diaphragmatic length-tension relationship is supported by the increases observed in VC, IC, and TLC with abdominal binders in tetraplegia.[90–93]

Maximal Static Inspiratory and Expiratory Mouth Pressures

Maximal mouth static respiratory pressures (MIP, MEP), considered surrogate measures of global inspiratory and expiratory muscle strength and more sensitive than spirometry for detection of early muscle weakness, are reduced among persons with tetraplegia, and in contrast to healthy subjects, MIP is higher than MEP due to greater compromise of expiratory muscle function.[54,94,95] Gounden[95] found a mean MEP in the sitting position of 48 cmH2O and mean MIP of −64 cmH2O among 30 subjects with C5–C8 complete motor lesions of more than 6 months' duration. Static mouth pressures correlated with level of injury among subjects with complete motor lesions, but not among those with incomplete lesions.[67]

Lung and Rib Cage Compliance

Synchronous contraction of neck muscles among subjects with high tetraplegia acts to pull the sternum cranially and to expand the upper rib cage,

but paradoxically results in inward displacement of the lateral walls of the lower rib cage.[20,96] Conversely, isolated diaphragmatic contraction is generally associated with expansion of the lower rib cage and collapse of the upper rib cage.[21,23,93,94,97–99] This abnormal coupling between the diaphragm and the upper rib cage is felt due to loss of intercostal muscle activity and increased compliance of the abdominal wall.[21,98,100,101] With time, this rib cage paradox decreases,[23] possibly because of the development of bony rib cage stiffness, increased strength of cervical accessory muscles, and improved coupling of various rib cage elements.[46] The increase in rib cage stiffness is thought to stem from ankylosis of joints due to chronic inability of subjects to inhale deeply and to increased spasticity of intercostal muscles.[46] In addition to reduction in rib cage compliance, there is a decrease in lung compliance that occurs within 1 month after injury that is felt more likely due to microatelectasis than to altered surfactant properties of the lungs.[23,46,53,54,100,102] Overall, decreases in chest wall and lung compliance coupled with increased abdominal wall compliance contribute to increased work of breathing in tetraplegia,[102–105] and possibly to respiratory muscle fatigue.[33]

RESPIRATORY SYMPTOMS

The symptom of breathlessness appears to be more prevalent among subjects with neurologically complete cervical SCI compared with those with lower-level injury. Using a modified respiratory symptom questionnaire developed for use in general epidemiologic studies among 180 subjects with SCI, breathlessness, the most prevalent symptom, was associated with level of injury: 73% in high tetraplegia (C5 and above not requiring chemical ventilation), 58% in low tetraplegia (C6 to C8), 43% in high paraplegia (T1–T7), and 29% in low paraplegia (T8–L3).[106] The prevalence of other symptoms, including chronic cough, phlegm, or wheeze, ranged from 18% to 30%, and did not differ significantly among the 4 groups. Of interest, in a subsequent analysis of the data, independent predictors of breathlessness were associated with level of injury and lung volume parameters (reduced TLC and ERV), whereas independent predictors of a combined symptom of cough + phlegm and/or wheeze were linked to smoking and FEV1 <60% predicted.[107] In other studies, breathlessness was more prevalent among those with neurologically complete cervical injury, those requiring a motorized wheelchair for daily activities, and those persons with SCI considered nonathletes.[108–110]

METHODS TO IMPROVE RESPIRATORY MUSCLE STRENGTH AND PULMONARY FUNCTION

Several interventional studies in persons with SCI have investigated whether inspiratory and expiratory resistive or threshold training, involving relatively inexpensive portable devices, are effective for improving respiratory muscle strength. Most studies have been uncontrolled and not comparable because of diverse protocols, heterogeneity of subject characteristics, or differences in training techniques. Since 2006, there have been 3 systematic reviews of respiratory muscle training in persons with SCI, and similar conclusions have been drawn; respiratory muscle training may realize increases in VC and static mouth pressures (MIP, MEP), although the effect size is small, and in many cases the data inconclusive.[111–113] Further, there is no evidence of carryover beyond the training. Insufficient data exist to make conclusions regarding the effects of respiratory muscle training on endurance, quality of life, exercise performance, or pulmonary complications.[111,113] In one well-designed trial, based on knowledge of residual function of expiratory muscles following cervical SCI, repetitive training of the clavicular portion of the pectoralis major via isometric exercise for 6 weeks among subjects with tetraplegia resulted in marked improvement in maximal isometric muscle strength and ERV, and a decrease in RV.[114] Also of interest, normocapnic hyperpnea, a technique that involves both inspiratory and expiratory muscle training via breathing at high minute ventilation, when compared with sham training for 8 weeks among 14 individuals with acute SCI, was associated with significant improvement in maximal voluntary ventilation and improved MIP and MEP.[115] The limitation of these techniques, however, lies in the difficulty in their implementation on a wider scale due to the substantive nature of the training and the methodologies involved. With regard to use of an abdominal binder to improve respiratory function, a systematic review and meta-analysis found a lack of sufficient evidence to either support or discourage use in persons with SCI.[116]

In highly motivated ventilator-dependent patients with SCI who have been shown to have intact phrenic nerve function, diaphragmatic pacing either by conventional thoracotomy and electrode placement directly upon the phrenic nerves, or via a newer and less invasive laparoscopic approach entailing insertion of electrodes directly into the diaphragm in proximity to the phrenic nerves, holds promise for achieving ventilator independence.[117,118] Preoperative testing by fluoroscopic evaluation of diaphragm

excursion during simultaneous phrenic nerve stimulation is generally required, as phrenic nerve damage is quite common in association with SCI, and precludes diaphragmatic pacing if present. After implantation, a period of diaphragm reconditioning is required. Although there are no randomized studies, significant improvement in quality of life has been reported, and success defined by either partial or complete freedom from ventilatory support is achieved in many subjects.[117,118] Surgical implantation of electrodes at T9, T11, and L1 levels also has been described to improve expiratory muscle function and cough effectiveness in highly selected patients.[119] Stimulated efforts achieve maximal airway pressures approaching that seen in the able-bodied, and with greater efficacy when compared with magnetic stimulation situated at T10 posteriorly or by placement of surface electrodes along the anterolateral abdominal wall. Implantation, however, is invasive and requires hemi-laminectomy along with attendant surgical risks.[119]

Preliminary investigations have been performed involving beta-2 adrenergic agonists to improve respiratory muscle strength in persons with SCI. Precedent comes from studies of oral beta-2 adrenergic agonist administration in young men eliciting anabolic effects on skeletal muscle,[120] and augmentation in muscle strength among patients with facioscapulohumeral muscular dystrophy.[121] In subjects with tetraplegia, oral beta-2 agonists were shown to amplify total work output during functional electrical stimulation of leg muscles,[122] and to improve forearm muscle size and strength.[123] On the basis of these reports, salmeterol, a long-acting beta-2 adrenergic agonist known to exhibit systemic absorption following inhalation,[124] was administered via inhalation (50 mcg twice daily) to 11 subjects with chronic stable tetraplegia in a randomized, double-blind, placebo-controlled, crossover trial. Significant improvements compared with matching placebo were seen in lung volumes (FVC, FEV1, ERV) and static mouth pressures (MIP and MEP) after 4 weeks of twice-daily administration, suggesting improvement in lung function and respiratory muscle strength (**Table 3**).[125] The medication was well tolerated, and no adverse events were reported.

Table 3
Effect of salmeterol on respiratory parameters among subjects with tetraplegia (n = 11)

Parameter	Baseline	Placebo	Salmeterol
FVC, L	3.11 ± 0.38	3.22 ± 0.41	3.36 ± 0.41[a,b]
FEV1, L	2.40 ± 0.51	2.52 ± 0.49	2.74 ± 0.52[a,b]
PEF, L/s	4.63 ± 1.13	5.01 ± 1.06	5.78 ± 1.20[a,b]
MIP, cmH_2O	−72.5 ± 18.6	−73.9 ± 21.5	−81.6 ± 20.8[a,b]
MEP, cmH_2O	40.9 ± 16.1	45.9 ± 19.2	51.3 ± 20.0[a,b]

The data are mean ± SD.

Abbreviations: FVC, forced vital capacity; FEV1, forced expired volume in 1 second; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PEF, peak expiratory flow.

[a] $P<.001$ compared with baseline.

[b] $P<.05$ compared with placebo.

Adapted from Grimm DR, Schilero GJ, Spungen AM, et al. Salmeterol improves pulmonary function in persons with tetraplegia. Lung 2006;184(6):338; with permission.

SLEEP-DISORDERED BREATHING

The prevalence of sleep-disordered breathing among subjects with tetraplegia has been reported to be as high as 83% in the first year following injury,[126] and among those with chronic injury in the range of 27% to 77%.[127–133] Reports of obstructive sleep apnea (OSA) predominate in the literature, although a recent investigation suggested a high prevalence of central apnea.[131] Symptom assessment as a tool to screen for OSA in this population appears to be relatively nondiscriminatory given the high prevalence of sleep disturbances reported regardless of cause.[131,134] The incidence of OSA among subjects with paraplegia does not appear different from that encountered in the general population, although the numbers of these subjects included in most studies are small. Possible etiologies for the high prevalence of sleep-disordered breathing among those with tetraplegia in addition to respiratory muscle weakness include sleep-related hypoventilation,[131] decreased pharyngeal cross-sectional area,[135] unopposed parasympathetic stimulation of mucosal and vessel walls of the upper airway,[136] preferential adoption of a supine sleeping position, loss of lean tissue mass and fat redistribution in the neck,[137] or compensatory neck muscle hypertrophy.[138] The long-term consequences of OSA in this population are not known, although treatment adherence with continuous positive airway pressure is low (20%–50%).[131,133,138,139]

REFERENCES

1. National Spinal Cord Injury Statistical Center, facts and figures at a glance. Birmingham (AL): University of Alabama at Birmingham; 2017. Available at: nscisc.uab.edu.

2. Chen Y, He Y, DeVivo MJ. Changing demographics and injury profile of new traumatic spinal cord injuries in the United States, 1972-2014. Arch Phys Med Rehabil 2016;97(10):1610–9.
3. Claxton AR, Wong DT, Chung F, et al. Predictors of hospital mortality and mechanical ventilation in patients with cervical spinal cord injury. Can J Anaesth 1998;45(2):144–9.
4. DeVivo MJ. Sir Ludwig Guttmann Lecture: trends in spinal cord injury rehabilitation outcomes from model systems in the United States: 1973-2006. Spinal Cord 2007;45(11):713–21.
5. DeVivo MJ, Jackson AB, Dijkers MP, et al. Current research outcomes from the model spinal cord injury care systems. Arch Phys Med Rehabil 1999;80(11):1363–4.
6. Lenehan B, Street J, Kwon BK, et al. The epidemiology of spinal cord injury in British Columbia, Canada. Spine (Phila Pa 1976) 2012;37(4):321–9.
7. Schoenfeld AJ, Sielski B, Rivera KP, et al. Epidemiology of cervical spine fractures in the US military. Spine J 2012;12(9):777–83.
8. Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. Spine (Phila Pa 1976) 2001;26(24 Suppl):S2–12.
9. Strauss DJ, Devivo MJ, Paculdo DR, et al. Trends in life expectancy after spinal cord injury. Arch Phys Med Rehabil 2006;87(8):1079–85.
10. Varma A, Hill EG, Nicholas J, et al. Predictors of early mortality after traumatic spinal cord injury; a population-based study. Spine 2010;35(7):778–83.
11. DeVivo MJ, Kartus PL, Stover SL, et al. Cause of death for patients with spinal cord injuries. Arch Intern Med 1989;149(8):1761–6.
12. Wuermser LA, Ho CH, Chiodo AE, et al. Spinal cord injury medicine. 2. Acute care management of traumatic and nontraumatic injury. Arch Phys Med Rehabil 2007;88(3 Suppl 1):S55–61.
13. Shavelle RM, DeVivo MJ, Brooks JC, et al. Improvements in long-term survival after spinal cord injury? Arch Phys Med Rehabil 2015;96(4):645–51.
14. Krause JS, Cao Y, DeVivo MJ, et al. Risk and protective factors for cause-specific mortality after spinal cord injury. Arch Phys Med Rehabil 2016; 97(10):1669–78.
15. van den Berg ME, Castellote JM, de Pedro-Cuesta J, et al. Survival after spinal cord injury: a systematic review. J Neurotrauma 2010;27(8): 1517–28.
16. Terson de Paleville DG, McKay WB, Folz RJ, et al. Respiratory motor control disrupted by spinal cord injury: mechanisms, evaluation, and restoration. Transl Stroke Res 2011;2(4):463–73.
17. Derenne JP, Macklem PT, Roussos C. The respiratory muscles: mechanics, control, and pathophysiology. Am Rev Respir Dis 1978;118(1):119–33.
18. Han JN, Gayan-Ramirez G, Dekhuijzen R, et al. Respiratory function of the rib cage muscles. Eur Respir J 1993;6(5):722–8.
19. Maarsingh EJ, van Eykern LA, Sprikkelman AB, et al. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. J Appl Physiol (1985) 2000; 88(6):1955–61.
20. De Troyer A, Estenne M, Vincken W. Rib cage motion and muscle use in high tetraplegics. Am Rev Respir Dis 1986;133(6):1115–9.
21. Estenne M, De Troyer A. Relationship between respiratory muscle electromyogram and rib cage motion in tetraplegia. Am Rev Respir Dis 1985;132(1): 53–9.
22. Manning H, McCool FD, Scharf SM, et al. Oxygen cost of resistive-loaded breathing in quadriplegia. J Appl Physiol (1985) 1992;73(3):825–31.
23. Scanlon PD, Loring SH, Pichurko BM, et al. Respiratory mechanics in acute quadriplegia. Lung and chest wall compliance and dimensional changes during respiratory maneuvers. Am Rev Respir Dis 1989;139(3):615–20.
24. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011;34(6):535–46.
25. Berlowitz DJ, Wadsworth B, Ross J. Respiratory problems and management in people with spinal cord injury. Breathe (Sheff) 2016;12(4): 328–40.
26. De Troyer A, Estenne M. The expiratory muscles in tetraplegia. Paraplegia 1991;29(6):359–63.
27. De Troyer A, Estenne M, Heilporn A. Mechanism of active expiration in tetraplegic subjects. N Engl J Med 1986;314(12):740–4.
28. Fujiwara T, Hara Y, Chino N. Expiratory function in complete tetraplegics: study of spirometry, maximal expiratory pressure, and muscle activity of pectoralis major and latissimus dorsi muscles. Am J Phys Med Rehabil 1999;78(5):464–9.
29. Bach JR. Noninvasive respiratory management of high level spinal cord injury. J Spinal Cord Med 2012;35(2):72–80.
30. Bach JR. Continuous noninvasive ventilation for patients with neuromuscular disease and spinal cord injury. Semin Respir Crit Care Med 2002; 23(3):283–92.
31. Slack RS, Shucart W. Respiratory dysfunction associated with traumatic injury to the central nervous system. Clin Chest Med 1994;15(4):739–49.
32. Bach JR. Noninvasive respiratory management and diaphragm and electrophrenic pacing in neuromuscular disease and spinal cord injury. Muscle Nerve 2013;47(2):297–305.
33. Brown R, DiMarco AF, Hoit JD, et al. Respiratory dysfunction and management in spinal cord

injury. Respir Care 2006;51(8):853–68 [discussion: 869–70].
34. Homnick DN. Mechanical insufflation-exsufflation for airway mucus clearance. Respir Care 2007; 52(10):1296–305 [discussion: 1306–7].
35. Reid WD, Brown JA, Konnyu KJ, et al. Physiotherapy secretion removal techniques in people with spinal cord injury: a systematic review. J Spinal Cord Med 2010;33(4):353–70.
36. Ditunno JF, Little JW, Tessler A, et al. Spinal shock revisited: a four-phase model. Spinal Cord 2004; 42(7):383–95.
37. Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. Am Rev Respir Dis 1981;124(1):41–4.
38. Haas F, Axen K, Pineda H, et al. Temporal pulmonary function changes in cervical cord injury. Arch Phys Med Rehabil 1985;66(3):139–44.
39. Mueller G, de Groot S, van der Woude L, et al. Time-courses of lung function and respiratory muscle pressure generating capacity after spinal cord injury: a prospective cohort study. J Rehabil Med 2008;40(4):269–76.
40. Bluechardt MH, Wiens M, Thomas SG, et al. Repeated measurements of pulmonary function following spinal cord injury. Paraplegia 1992; 30(11):768–74.
41. Axen K, Pineda H, Shunfenthal I, et al. Diaphragmatic function following cervical cord injury: neurally mediated improvement. Arch Phys Med Rehabil 1985;66(4):219–22.
42. McKinley W, McNamee S, Meade M, et al. Incidence, etiology, and risk factors for fever following acute spinal cord injury. J Spinal Cord Med 2006; 29(5):501–6.
43. McMichan JC, Michel L, Westbrook PR. Pulmonary dysfunction following traumatic quadriplegia. Recognition, prevention, and treatment. JAMA 1980;243(6):528–31.
44. Oo T, Watt JW, Soni BM, et al. Delayed diaphragm recovery in 12 patients after high cervical spinal cord injury. A retrospective review of the diaphragm status of 107 patients ventilated after acute spinal cord injury. Spinal Cord 1999;37(2):117–22.
45. Frisbie JH, Binard J. Low prevalence of prostatic cancer among myelopathy patients. J Am Paraplegia Soc 1994;17(3):148–9.
46. Estenne M, De Troyer A. The effects of tetraplegia on chest wall statics. Am Rev Respir Dis 1986; 134(1):121–4.
47. Garshick E, Ashba J, Tun CG, et al. Assessment of stature in spinal cord injury. J Spinal Cord Med 1997;20(1):36–42.
48. Ashba J, Garshick E, Tun CG, et al. Spirometry–acceptability and reproducibility in spinal cord injured subjects. J Am Paraplegia Soc 1993; 16(4):197–203.
49. Kelley A, Garshick E, Gross ER, et al. Spirometry testing standards in spinal cord injury. Chest 2003;123(3):725–30.
50. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2): 319–38.
51. Tully K, Koke K, Garshick E, et al. Maximal expiratory pressures in spinal cord injury using two mouthpieces. Chest 1997;112(1):113–6.
52. Almenoff PL, Spungen AM, Lesser M, et al. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. Lung 1995;173(5):297–306.
53. Forner JV. Lung volumes and mechanics of breathing in tetraplegics. Paraplegia 1980;18(4):258–66.
54. Fugl-Meyer AR, Grimby G. Ventilatory function in tetraplegic patients. Scand J Rehabil Med 1971; 3(4):151–60.
55. Hemingway A, Bors E, Hobby RP. An investigation of the pulmonary function of paraplegics. J Clin Invest 1958;37(5):773–82.
56. Kokkola K, Moller K, Lehtonen T. Pulmonary function in tetraplegic and paraplegic patients. Ann Clin Res 1975;7(2):76–9.
57. Linn WS, Adkins RH, Gong H Jr, et al. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. Arch Phys Med Rehabil 2000;81(6): 757–63.
58. Linn WS, Spungen AM, Gong H Jr, et al. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. Spinal Cord 2001;39(5): 263–8.
59. Ohry A, Molho M, Rozin R. Alterations of pulmonary function in spinal cord injured patients. Paraplegia 1975;13(2):101–8.
60. Roth EJ, Nussbaum SB, Berkowitz M, et al. Pulmonary function testing in spinal cord injury: correlation with vital capacity. Paraplegia 1995;33(8): 454–7.
61. Fugl-Meyer AR. Effects of respiratory muscle paralysis in tetraplegic and paraplegic patients. Scand J Rehabil Med 1971;3(4):141–50.
62. Jain NB, Brown R, Tun CG, et al. Determinants of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC in chronic spinal cord injury. Arch Phys Med Rehabil 2006;87(10):1327–33.
63. Linn WS, Spungen AM, Gong H Jr, et al. Smoking and obstructive lung dysfunction in persons with chronic spinal cord injury. J Spinal Cord Med 2003;26(1):28–35.
64. Stepp EL, Brown R, Tun CG, et al. Determinants of lung volumes in chronic spinal cord injury. Arch Phys Med Rehabil 2008;89(8):1499–506.
65. Schilero GJ, Hobson JC, Singh K, et al. Bronchodilator effects of ipratropium bromide and albuterol

sulfate among subjects with tetraplegia. J Spinal Cord Med 2018;41(1):42–7.
66. Radulovic M, Schilero GJ, Wecht JM, et al. Airflow obstruction and reversibility in spinal cord injury: evidence for functional sympathetic innervation. Arch Phys Med Rehabil 2008;89(12):2349–53.
67. Mateus SR, Beraldo PS, Horan TA. Cholinergic bronchomotor tone and airway caliber in tetraplegic patients. Spinal Cord 2006;44(5):269–74.
68. Schilero GJ, Grimm DR, Bauman WA, et al. Assessment of airway caliber and bronchodilator responsiveness in subjects with spinal cord injury. Chest 2005;127(1):149–55.
69. Schilero GJ, Grimm D, Spungen AM, et al. Bronchodilator responses to metaproterenol sulfate among subjects with spinal cord injury. J Rehabil Res Dev 2004;41(1):59–64.
70. Spungen AM, Dicpinigaitis PV, Almenoff PL, et al. Pulmonary obstruction in individuals with cervical spinal cord lesions unmasked by bronchodilator administration. Paraplegia 1993;31(6):404–7.
71. Laitinen A, Partanen M, Hervonen A, et al. Electron microscopic study on the innervation of the human lower respiratory tract: evidence of adrenergic nerves. Eur J Respir Dis 1985;67(3):209–15.
72. Partanen M, Laitinen A, Hervonen A, et al. Catecholamine- and acetylcholinesterase-containing nerves in human lower respiratory tract. Histochemistry 1982;76(2):175–88.
73. Vigil L, Calaf N, Codina E, et al. Video-assisted sympathectomy for essential hyperhidrosis: effects on cardiopulmonary function. Chest 2005;128(4):2702–5.
74. Tseng MY, Tseng JH. Thoracoscopic sympathectomy for palmar hyperhidrosis: effects on pulmonary function. J Clin Neurosci 2001;8(6):539–41.
75. Noppen M, Vincken W. Thoracoscopic sympathicolysis for essential hyperhidrosis: effects on pulmonary function. Eur Respir J 1996;9(8):1660–4.
76. Grimm DR, Arias E, Lesser M, et al. Airway hyperresponsiveness to ultrasonically nebulized distilled water in subjects with tetraplegia. J Appl Physiol (1985) 1999;86(4):1165–9.
77. Fein ED, Grimm DR, Lesser M, et al. The effects of ipratropium bromide on histamine-induced bronchoconstriction in subjects with cervical spinal cord injury. J Asthma 1998;35(1):49–55.
78. Singas E, Lesser M, Spungen AM, et al. Airway hyperresponsiveness to methacholine in subjects with spinal cord injury. Chest 1996;110(4):911–5.
79. Dicpinigaitis PV, Spungen AM, Bauman WA, et al. Bronchial hyperresponsiveness after cervical spinal cord injury. Chest 1994;105(4):1073–6.
80. Grimm DR, Chandy D, Almenoff PL, et al. Airway hyperreactivity in subjects with tetraplegia is associated with reduced baseline airway caliber. Chest 2000;118(5):1397–404.
81. Cockcroft DW, Davis BE. The bronchoprotective effect of inhaling methacholine by using total lung capacity inspirations has a marked influence on the interpretation of the test result. J Allergy Clin Immunol 2006;117(6):1244–8.
82. DeLuca RV, Grimm DR, Lesser M, et al. Effects of a beta2-agonist on airway hyperreactivity in subjects with cervical spinal cord injury. Chest 1999;115(6):1533–8.
83. Singas E, Grimm DR, Almenoff PL, et al. Inhibition of airway hyperreactivity by oxybutynin chloride in subjects with cervical spinal cord injury. Spinal Cord 1999;37(4):279–83.
84. Grimm DR, DeLuca RV, Lesser M, et al. Effects of GABA-B agonist baclofen on bronchial hyperreactivity to inhaled histamine in subjects with cervical spinal cord injury. Lung 1997;175(5):333–41.
85. Cragg JJ, Warner FM, Kramer JK, et al. A Canada-wide survey of chronic respiratory disease and spinal cord injury. Neurology 2015;84(13):1341–5.
86. Ali J, Qi W. Pulmonary function and posture in traumatic quadriplegia. J Trauma 1995;39(2):334–7.
87. Baydur A, Adkins RH, Milic-Emili J. Lung mechanics in individuals with spinal cord injury: effects of injury level and posture. J Appl Physiol (1985) 2001;90(2):405–11.
88. Chen CF, Lien IN, Wu MC. Respiratory function in patients with spinal cord injuries: effects of posture. Paraplegia 1990;28(2):81–6.
89. Estenne M, De Troyer A. Mechanism of the postural dependence of vital capacity in tetraplegic subjects. Am Rev Respir Dis 1987;135(2):367–71.
90. Goldman JM, Rose LS, Williams SJ, et al. Effect of abdominal binders on breathing in tetraplegic patients. Thorax 1986;41(12):940–5.
91. Hart N, Laffont I, de la Sota AP, et al. Respiratory effects of combined truncal and abdominal support in patients with spinal cord injury. Arch Phys Med Rehabil 2005;86(7):1447–51.
92. Maloney FP. Pulmonary function in quadriplegia: effects of a corset. Arch Phys Med Rehabil 1979;60(6):261–5.
93. McCool FD, Pichurko BM, Slutsky AS, et al. Changes in lung volume and rib cage configuration with abdominal binding in quadriplegia. J Appl Physiol (1985) 1986;60(4):1198–202.
94. Fugl-Meyer AR, Grimby G. Rib-cage and abdominal volume ventilation partitioning in tetraplegic patients. Scand J Rehabil Med 1971;3(4):161–7.
95. Gounden P. Static respiratory pressures in patients with post-traumatic tetraplegia. Spinal Cord 1997;35(1):43–7.
96. Danon J, Druz WS, Goldberg NB, et al. Function of the isolated paced diaphragm and the cervical accessory muscles in C1 quadriplegics. Am Rev Respir Dis 1979;119(6):909–19.

97. Mead J, Banzett RB, Lehr J, et al. Effect of posture on upper and lower rib cage motion and tidal volume during diaphragm pacing. Am Rev Respir Dis 1984;130(2):320–1.
98. Moulton A, Silver JR. Chest movements in patients with traumatic injuries of the cervical cord. Clin Sci 1970;39(3):407–22.
99. Urmey W, Loring S, Mead J, et al. Upper and lower rib cage deformation during breathing in quadriplegics. J Appl Physiol (1985) 1986;60(2):618–22.
100. De Troyer A, Heilporn A. Respiratory mechanics in quadriplegia. The respiratory function of the intercostal muscles. Am Rev Respir Dis 1980;122(4):591–600.
101. Goldman MD, Mead J. Mechanical interaction between the diaphragm and rib cage. J Appl Physiol 1973;35(2):197–204.
102. Stone DJ, Keltz H. The effect of respiratory muscle dysfunction on pulmonary function. Studies in patients with spinal cord injuries. Am Rev Respir Dis 1963;88:621–9.
103. Bergofsky EH. Quantiation of the function of respiratory muscles in normal individuals and quadriplegic patients. Arch Phys Med Rehabil 1964;45:575–80.
104. Bergofsky EH. Mechanism for respiratory insufficiency after cervical cord injury; a source of alveolar hypoventilation. Ann Intern Med 1964;61:435–47.
105. Silver JR. The oxygen cost of breathing in tetraplegic patients. Paraplegia 1963;1:204–14.
106. Spungen AM, Grimm DR, Lesser M, et al. Self-reported prevalence of pulmonary symptoms in subjects with spinal cord injury. Spinal Cord 1997;35(10):652–7.
107. Spungen AM, Grimm DR, Schilero G, et al. Relationship of respiratory symptoms with smoking status and pulmonary function in chronic spinal cord injury. J Spinal Cord Med 2002;25(1):23–7.
108. Ayas NT, DiMarco AF, Hoit JD, et al. Breathlessness in spinal cord injury depends on injury level. J Spinal Cord Med 1999;22(2):97–101.
109. Grandas NF, Jain NB, Denckla JB, et al. Dyspnea during daily activities in chronic spinal cord injury. Arch Phys Med Rehabil 2005;86(8):1631–5.
110. Wien MF, Garshick E, Tun CG, et al. Breathlessness and exercise in spinal cord injury. J Spinal Cord Med 1999;22(4):297–302.
111. Berlowitz DJ, Tamplin J. Respiratory muscle training for cervical spinal cord injury. Cochrane Database Syst Rev 2013;(7):CD008507.
112. Sheel AW, Reid WD, Townson AF, et al. Effects of exercise training and inspiratory muscle training in spinal cord injury: a systematic review. J Spinal Cord Med 2008;31(5):500–8.
113. Van Houtte S, Vanlandewijck Y, Gosselink R. Respiratory muscle training in persons with spinal cord injury: a systematic review. Respir Med 2006;100(11):1886–95.
114. Estenne M, Knoop C, Vanvaerenbergh J, et al. The effect of pectoralis muscle training in tetraplegic subjects. Am Rev Respir Dis 1989;139(5):1218–22.
115. Van Houtte S, Vanlandewijck Y, Kiekens C, et al. Patients with acute spinal cord injury benefit from normocapnic hyperpnoea training. J Rehabil Med 2008;40(2):119–25.
116. Wadsworth BM, Haines TP, Cornwell PL, et al. Abdominal binder use in people with spinal cord injuries: a systematic review and meta-analysis. Spinal Cord 2009;47(4):274–85.
117. DiMarco AF, Onders RP, Ignagni A, et al. Inspiratory muscle pacing in spinal cord injury: case report and clinical commentary. J Spinal Cord Med 2006;29(2):95–108.
118. Le Pimpec-Barthes F, Legras A, Arame A, et al. Diaphragm pacing: the state of the art. J Thorac Dis 2016;8(Suppl 4):S376–86.
119. DiMarco AF, Kowalski KE, Geertman RT, et al. Lower thoracic spinal cord stimulation to restore cough in patients with spinal cord injury: results of a National Institutes of Health-sponsored clinical trial. Part I: methodology and effectiveness of expiratory muscle activation. Arch Phys Med Rehabil 2009;90(5):717–25.
120. Martineau L, Horan MA, Rothwell NJ, et al. Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men. Clin Sci (Lond) 1992;83(5):615–21.
121. Kissel JT, McDermott MP, Natarajan R, et al. Pilot trial of albuterol in facioscapulohumeral muscular dystrophy. FSH-DY Group. Neurology 1998;50(5):1402–6.
122. Murphy RJ, Hartkopp A, Gardiner PF, et al. Salbutamol effect in spinal cord injured individuals undergoing functional electrical stimulation training. Arch Phys Med Rehabil 1999;80(10):1264–7.
123. Signorile JF, Banovac K, Gomez M, et al. Increased muscle strength in paralyzed patients after spinal cord injury: effect of beta-2 adrenergic agonist. Arch Phys Med Rehabil 1995;76(1):55–8.
124. Bennett JA, Harrison TW, Tattersfield AE. The contribution of the swallowed fraction of an inhaled dose of salmeterol to it systemic effects. Eur Respir J 1999;13(2):445–8.
125. Grimm DR, Schilero GJ, Spungen AM, et al. Salmeterol improves pulmonary function in persons with tetraplegia. Lung 2006;184(6):335–9.
126. Berlowitz DJ, Brown DJ, Campbell DA, et al. A longitudinal evaluation of sleep and breathing in the first year after cervical spinal cord injury. Arch Phys Med Rehabil 2005;86(6):1193–9.
127. Berlowitz DJ, Spong J, Gordon I, et al. Relationships between objective sleep indices and symptoms in a community sample of people with

tetraplegia. Arch Phys Med Rehabil 2012;93(7):1246–52.

128. Burns SP, Little JW, Hussey JD, et al. Sleep apnea syndrome in chronic spinal cord injury: associated factors and treatment. Arch Phys Med Rehabil 2000;81(10):1334–9.
129. Leduc BE, Dagher JH, Mayer P, et al. Estimated prevalence of obstructive sleep apnea-hypopnea syndrome after cervical cord injury. Arch Phys Med Rehabil 2007;88(3):333–7.
130. McEvoy RD, Mykytyn I, Sajkov D, et al. Sleep apnoea in patients with quadriplegia. Thorax 1995;50(6):613–9.
131. Sankari A, Bascom A, Sowmini O, et al. Sleep disordered breathing in chronic spinal cord injury. J Clin Sleep Med 2014;10(1):65–72.
132. Short DJ, Stradling JR, Williams SJ. Prevalence of sleep apnoea in patients over 40 years of age with spinal cord lesions. J Neurol Neurosurg Psychiatry 1992;55(11):1032–6.
133. Stockhammer E, Tobon A, Michel F, et al. Characteristics of sleep apnea syndrome in tetraplegic patients. Spinal Cord 2002;40(6):286–94.
134. Biering-Sorensen F, Biering-Sorensen M. Sleep disturbances in the spinal cord injured: an epidemiological questionnaire investigation, including a normal population. Spinal Cord 2001;39(10):505–13.
135. Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. Am Rev Respir Dis 1984;130(2):175–8.
136. Wasicko MJ, Hutt DA, Parisi RA, et al. The role of vascular tone in the control of upper airway collapsibility. Am Rev Respir Dis 1990;141(6):1569–77.
137. Spungen AM, Adkins RH, Stewart CA, et al. Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. J Appl Physiol (1985) 2003;95(6):2398–407.
138. Burns SP, Kapur V, Yin KS, et al. Factors associated with sleep apnea in men with spinal cord injury: a population-based case-control study. Spinal Cord 2001;39(1):15–22.
139. Berlowitz DJ, Spong J, Pierce RJ, et al. The feasibility of using auto-titrating continuous positive airway pressure to treat obstructive sleep apnoea after acute tetraplegia. Spinal Cord 2009;47(12):868–73.