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Respiratory Motor Control Disrupted by Spinal Cord Injury: Mechanisms, Evaluation, and Restoration

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Abstract

Pulmonary complications associated with persistent respiratory muscle weakness, paralysis, and spasticity are among the most important problems faced by patients with spinal cord injury when lack of muscle strength and disorganization of reciprocal respiratory muscle control lead to breathing insufficiency. This review describes the mechanisms of the respiratory motor control and its change in individuals with spinal cord injury, methods by which respiratory function is measured, and rehabilitative treatment used to restore respiratory function in those who have experienced such injury.

Keywords

Spinal cord injury; Motor control; Respiratory muscles; Respiratory function; Rehabilitation

Introduction

Breathing is an essential life-sustaining activity that requires the contraction of respiratory muscles, coordinated by the respiratory motor control system which, when healthy, integrates input from the brain, brainstem, spinal cord, and peripheral nerves. Traumatic disruption of this circuitry as often occurs with spinal cord injury (SCI) presents a complex problem for clinicians who must respond to the degree to which respiratory function is impaired in order to maintain life and improve its quality. SCI devastates the lives of approximately 12,000 people in the USA each year leaving a population of approximately 300,000 individuals with chronic SCI [1, 2]. In the acute phase of injury, 36% to 83% of SCI patients experience serious respiratory complications [3, 4] and, even in the chronic phase of

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recovery from SCI, the focus of this review, respiratory complications are among the leading causes of death [5].

Trauma to the spinal cord causes the loss of motor neurons, interneurons, myelin insulation provided by oligodendrocytes, and ascending and descending long-tract axons within the injury zone that can spread over multiple segments [6]. Thus, sensory input, motor output, and central processing are disrupted in ways that vary considerably across the population. When SCI alters the control of trunk muscles, respiratory motor control is compromised [7], leading to secondary debilitating effects that impact recovery [8, 9] and quality of life [10].

The following review will describe the mechanics and physiological goals of respiration, the muscles used, and their neural control in both uninjured people and those with non-ventilator-dependent SCI. It will review the methods by which respiratory function is measured. Finally, it will cover rehabilitative treatment used to restore respiratory function in those who have experienced spinal cord injury.

Respiratory Function in the Non-injured Population

The primary role of the respiratory system is to bring in air rich with oxygen and to exhale air with carbon dioxide from the alveolar gas exchange process in order to keep arterial blood gasses within the acceptable values for life [11]. Oxygen within the inhaled air travels through the airways to the alveoli in the lungs where it diffuses into pulmonary capillary blood and binds with hemoglobin to be carried to other tissues of the body where it will be utilized in metabolic reactions. Venous blood contains higher concentrations of carbon dioxide which itself is being transported in three distinct forms: 10% is dissolved in plasma, 20% is bound to hemoglobin, and about 70% exists as bicarbonate. Once in the lungs, carbon dioxide diffuses through the alveoli and then is expelled during expiration. The process of taking in fresh, oxygen-rich air and exhaling the gaseous products of metabolism is regulated by the central nervous system and accomplished through the controlled contractions of numerous respiratory muscle groups [12].

Muscles and Mechanics of Respiration

Respiratory muscles are skeletal muscles whose primary role is to displace the chest wall rhythmically to inspire air rich with oxygen and to expire air with high content of carbon dioxide. Table 1 lists the muscles generally considered to be used for breathing along with their innervation and actions. These muscles work synergistically, and their function is related to the mechanics of the chest wall. In humans, the trunk consists of the rib cage and the abdomen, separated by the diaphragm. The rib cage consists of a complex bony structure, cartilage, and several skeletal muscles. Components of the rib cage include the thoracic vertebrae, the ribs, costal cartilages, sternum, and all the articulations and ligaments that allow a variety of movements. There are 12 pairs of ribs; the first 7 pairs (vertebrosternal ribs) attach directly to the sternum, the following 3 pairs (vertebrochondral ribs) attach indirectly to sternum, and the lowest 2 pairs are the floating ribs (vertebral ribs) and their ends are free. The dorsal ends of the ribs are attached to the vertebra by ligaments, and the ventral ends of the non-floating ribs are joined to the sternum directly or indirectly by cartilaginous articulations. The costosternal attachments are shorter and more restrictive in the upper than in the lower ribs, allowing the latter ones to have more freedom of movement.

Breathing is often described as being of two types: quiet breathing (at rest) and forced breathing. The diaphragm and the external intercostals are the prime movers for quiet inspiration. As ventilatory demands increase, for example during exercise, other accessory muscles for inspiration are recruited [13–15]. The accessory muscles used for inspiration

include: sternocleidomastoid, scalenes, and upper trapezius. In humans, expiration has been largely assumed to be a passive process since it is usually examined during resting breathing in the supine position [11]. Nevertheless, during forced expiration, muscles that depress the ribs and reduce the thoracic cavity (i.e., expiratory muscles) are recruited. Expiratory muscles include: internal intercostals, rectus abdominis, external and internal obliques. Additionally, other muscles, such as pectoralis major [13, 16] and latissimus dorsi [16], may be recruited for expiratory tasks.

Muscles that Perform Inspiration

The *diaphragm* is the major muscle contributing to inspiration. The vertebral (crural) portion of the diaphragm inserts on the anterolateral aspect of the first three lumbar vertebrae and on the aponeurotic arcuate ligaments; the fibers of the costal portion insert on the xyphoid process of the sternum and the upper margins of the lower six ribs [11]. The diaphragm is shaped like a dome, with a centrally located tendon, and a zone of apposition, directly apposed to the inner aspect of the lower ribs. The apposition zone constitutes 30% of the total surface area of the rib cage. During inspiration, as muscle fibers shorten, the apposed area decreases and the dome descends axially, increasing the thoracic cavity and displacing the abdominal contents caudally. The diaphragm is innervated by the phrenic nerves which arise from cervical nerve roots C_3 to C_5.

Intercostal muscles are found in two very thin layers separated by an irregular aponeurotic membrane [17]. The external intercostals are superficial to the internal intercostals. These muscles are innervated by the corresponding thoracic spinal nerves. The external intercostals and the parasternal part of internal intercostals have inspiratory actions, and the interosseus part of the internal intercostal has expiratory action [14, 17]. The external intercostals have a synergistic action with diaphragm during inspiration [18]. Each external intercostal attaches from the inferior border of one rib to the superior border of the rib directly inferior. The fibers of the external intercostal slope obliquely, caudal and ventrally from the rib above to the one below (front pocket). The major respiratory action of the external intercostal is to elevate from the 2nd to the 12th ribs at the sternocostal and costospinal joints. De Troyer et al. [19] reported that both internal and external intercostals have a net-lowering action on the ribs, and that the same directional rib motion was obtained when stimulating either intercostal group.

Muscles that Perform Expiration

Internal intercostals are located in the intercostal spaces of ribs 1 through 12 [18, 20]. As with the external intercostals, these muscles are innervated by the corresponding thoracic spinal nerves. Fibers of the internal intercostals have the opposite orientation of the external intercostals (back pocket) [17]. Each internal intercostal connects the superior border of one rib and its costal cartilage to the inferior border of the rib and its costal cartilage that is directly superior. The major respiratory action of the internal intercostals is to lower ribs (from the 2nd to the 12th ribs) at the sternocostal and costospinal joints.

Rectus abdominis is an abdominal muscle active in forced expiration. This muscle originates from the ventral aspect of the fifth, sixth, and seventh costal cartilages and the sternum. It is innervated by the lower thoracic nerves T_5–T_{12} [11].

External and internal oblique muscles are used during forced expiration. The external oblique is the most superficial and originates in the lower eight ribs and intercostals, and its fibers run in an oblique line inferiorly and posteriorly to the iliac crest and the inguinal ligament. It is innervated by the lower six intercostal nerves. Underneath the external oblique lies the internal oblique. Its fibers run perpendicular to the external oblique. It is

innervated by the lower intercostal nerves, as well as the iliohypogastric and the ilioinguinal nerve [21].

Accessory Muscles of Respiration

Accessory muscles are recruited when the ventilatory demands are higher than normal. Accessory muscles of inspiration include the *sternocleidomastoid*, *scalenes*, and *upper trapezius* [20]. Muscles being innervated by the cranial XI or spinal accessory nerve receive the name of accessory muscles of inspiration. Cranial nerve XI has two parts: the cranial and the spinal parts. The spinal part innervates the sternocleidomastoid and the upper trapezius. Scalenes are considered accessory muscles for inspiration, even though they are innervated by cervical spinal nerves [11]. Other muscles have been reported to contribute to breathing, but their actions are still unclear. These muscles include: upper trapezius, pectoralis [22, 23], latissimus dorsi [16, 24], and serratus anterior [25].

Motor Control of Respiration

Our understanding of the control of breathing has largely been derived from studies performed in animal models. Most of these studies of respiratory control have focused on the unconscious regularly repeating activation of the motor neurons innervated by the phrenic nerve to elicit contractions from the diaphragm and internal intercostal muscles [26] to draw air into the lungs. This and related literature have focused on the identification and characterization of central rhythm and pattern generation processes carried out in the rostroventral medulla in which the inspiratory oscillator is dominant [27]. The regulation of respiratory rate by this oscillator is largely in response to the concentrations of gasses in the blood [28]. However, emotional events and volitional efforts can modify the behavior of this oscillator through fibers from the limbic and corticobulbar pathways, respectively [29]. On the other hand, output of the expiratory leg of this oscillator becomes faster only during increased respiratory effort such as would occur under hypercapnic conditions [30].

The mechanisms by which respiratory rate is regulated have been heavily studied and are well accepted [31]. Of interest for this review are the mechanisms that modulate motor unit activation in the muscles of respiration beyond chemoreceptor influenced automatic rate control, especially those that can be impacted by SCI. However, in order to do so, perspective needs to be established. The final common path for motor output from the central nervous system is the motor unit which is made up of the spinal motor neuron, its axon, neuromuscular junctions, and the muscle fibers it activates. This is true for all motor output whether it be for the purpose of moving limbs or filling and emptying the lungs. Thus, the measurement and analysis of motor output from electromyographic signals, recorded motor unit potentials whether via surface or needle electrodes, allow the description and study of motor control in humans. Also, common to all spinal motor neurons involved in limb movement and demonstrated largely in cat models is that they receive excitatory and inhibitory input via sometimes direct but more often indirect interneuronal processing circuitry from local and distant, peripheral and central sources [32–35]. There is also evidence that there is considerable interneuronal processing involved in the organization of motor outflow for respiration [31, 36].

Again in the cat model, Davies and coworkers [26] determined that approximately half of the bulbospinal neurons from the previously described oscillator ended within multiple spinal segments and synapsed directly on phrenic motor neurons and suggested that most motor unit depolarization was the result of interneuronal activity. In addition, vestibulospinal fibers synapsing in propriospinal interneurons have been shown to alter phrenic nerve activity [37], and postural changes altered spontaneous activity in the diaphragm and abdominal muscles [38]. Further, it has been shown that peripheral nerve

input from sensory end organs in the trachea and lungs [39] and muscles [19, 36, 40–42] can alter spinal motor output to the muscles of respiration.

Another group of inputs to spinal motor processing are those arriving from the brain via the corticospinal system. Such connections allow for volitional control of inspiration and expiration for speaking, singing, and other goal-directed tasks. These oligosynaptic connections have been demonstrated in humans using transcranial electrical or magnetic motor cortex stimulation. Gandevia and Rothwell [43] showed that electrical stimulation through two electrodes placed one over the scalp vertex and the other 1 cm anterior and 6–7 cm anterior to it elicited a twitch from the diaphragm in three healthy subjects. In addition, it was shown that this transcranially induced motor-evoked potential (MEP) from the diaphragm could be facilitated during volitional inspiration as are the MEPs from limb muscles by volitional contraction [44] and that transcranial magnetic motor cortex stimulation (TMS)-induced MEPs were reduced during sleep when cortical excitability was reduced [45]. TMS was also used to demonstrate the direct or near-direct corticospinal connections between the motor cortex and spinal motor neurons for intercostal [46, 47], pectoralis [48], rectus abdominus [49], oblique [50], and paraspinal [51] muscles. Finally, bilateral activation of abdominal muscles by TMS suggested that there may be a greater degree of uncrossed corticospinal innervation for abdominal muscles than is found for limb muscles [52]. Thus, spinal motor neurons whose axons connect to muscles of respiration find themselves responding to a variety of demonstrable central and peripheral excitatory and inhibitory inputs that are processed into organized output by a plurisegmental interneuronal circuitry.

Measurements of Pulmonary Function

Spirometry, Maximal Inspiratory, and Expiratory Pressure Measurements

Routine measurements of the mechanical properties of respiratory function, that is, volumes and flows of breathing air presented as a percent of predicted values [53], are nonspecific in relation to the evaluation of respiratory motor control but give useful indirect information about respiratory muscle performance [54]. Traditionally, parameters that quantify respiratory motor function such as peak flow, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), maximal expiratory pressure (PE_{max}), maximal inspiratory pressure (PI_{max}), and transdiaphragmatic pressure have been used in clinical and research testing to measure the strength of respiratory muscles [55, 56]. The maximal voluntary ventilation measurement was previously recommended for measuring neuromuscular weakness, but in practice, there is a proportionate reduction in vital capacity and may provide additional information in extrapyramidally comprised individuals [54]. Sniff nasal inspiratory pressure may provide similar information as the PI_{max} but has the advantage of being easier to perform [57].

The PE_{max} and PI_{max} testing is performed against a blocked airway [58], and as such helps assess the aggregate force respiratory muscles can generate. PI_{max} is a metric of diaphragm strength, whereas PE_{max} is a metric of combined force generated by abdominal and intercostal muscle. Maximal inspiratory pressure is measured from near residual volume, and maximal expiratory pressure is measured at or near total lung capacity. The assessment of maximal pressures requires a sharp, forceful effort maintained for a minimum of 2 s. The maximum pressure for each is taken as the highest value that can be sustained for a minimum of 1 s [54]. The pressure meter should incorporate a 1-mm leak to reduce buccal muscle contribution during the maximal expiratory pressure [58, 59]. Absolute contraindications for performing maximum respiratory pressures tests include unstable angina, recent (<4 weeks) myocardial infarction, recent pneumothorax, uncontrolled hypertension, and lung biopsy within the previous week [54, 60].

Measurements of the Respiratory Motor Control

Electromyography (EMG) is an essential neurophysiological technique in neuromuscular physiology whether recorded from electrodes placed within a muscle [61, 62] or on the skin surface over a muscle or group of muscles [61, 63, 64]. It also helps the clinician or researcher to accurately diagnose neurological disorders [65]. For limb muscles, EMG is also an effective tool for characterizing severity of damage to central nervous system motor control [66–69], elucidating evidence of minimal motor control [70, 71], measuring inappropriate muscle activation [72, 73], and tracking recovery [74] and the effects of therapy [68, 75–77].

Electromyography of Respiratory Muscles

A number of investigations have suggested that there is a correlation between pulmonary function and the neural activation of muscles involved in respiration [16, 78–80]. Peak expiratory flow rate was shown to correlate with the EMG activity of pectoralis major and latissimus dorsi muscles [16, 24]. EMG of intercostal muscles shows significant increases with incrementally increased respiratory loads in inspiratory muscle endurance tests in healthy female individuals, while the activity of the seternocleidomastoid muscles does not [78]. This is similar to the findings of Yokoba and coworkers [79] in healthy individuals, in which sternocleidomastoid muscles start to contract at around 34% of the maximal inspiratory pressure. In addition, they found that scalenes and tranversus abdominis EMG activity showed a significant linear correlation (R^2, 0.98) during gradual production of expiratory and inspiratory mouth pressure to maximal. Similarly, EMG activity of the sternocleidomastoid showed a strong linear correlation with maximal inspiratory pressure (R^2, 0.97) and trapezius, a nonlinear correlation (R^2, 0.50). Further, trapezius is recruited at 90% of the maximal inspiratory mouth pressure. EMG activity of parasternal intercostals, triangularis sterni [13], and scalene muscles in anesthetized dogs increases as lung volume increases during inspiration. Further, lower and upper abdominal muscles, external obliques, and transverses abdominis are electrically active when expiration occurs [11].

Respiratory Motor Control After SCI

The goal of basic SCI research is to improve disrupted motor function including respiratory motor control. This research has focused on several areas including regeneration through peripheral nerve grafts and sprouting, activation and maintenance of crossed phrenic pathways, and the initiation of long-term synaptic plasticity. However, since none of these approaches have reached clinical application yet, it is evident that more research is needed to address all of the questions surrounding the neural control of respiratory function following SCI [81]. Spinal cord injury that damages long-tract fibers disrupts, to varying degrees, the transmission of impulses traveling to and from this spinal circuitry. However, methods for assessing the impact of SCI on motor control of respiration have been limited. Considerable work has been done to demonstrate that SCI reduces lung volumes and respiratory flow rates [8, 82, 83] and that the degree of disruption was related to the injury level [69, 84]. However, due to the multiple spinal levels of innervation for the muscles of respiration, and that the currently accepted clinical scale for measuring injury severity and level, the American Spinal Injury Association Impairment Scale (AIS), they cannot characterize trunk and respiratory muscle function. It has been shown that most human SCI lesions are to some degree incomplete [6, 70, 71] which is also true for respiratory motor control [85]. Further, the unintended and unwanted muscle activity or spasticity experienced by many people with spinal cord injuries can also impair respiratory function [9, 69, 86]. Thus, the evaluation of motor control of respiration is as yet not well developed [69].

Effect of SCI on Respiratory Function

Symptoms of respiratory insufficiency are highly correlated with the level and severity of the spinal lesion [82, 87]. Injury to the cervical or thoracic spinal cord affects spinal nerves that innervate respiratory muscles. The more rostral the level of injury, the more significant the respiratory impairment [69, 88]. Spirometrical values of FVC and FEV_1 increase with more caudal lesions [7, 82]. Severity of the spinal cord lesion is related to decreased functional residual capacity, total lung capacity, expiratory reserve volumes, and increased residual volumes [89]. Individuals with complete or incomplete SCI often suffer from these respiratory insufficiencies due to paralysis [55, 56, 90, 91], muscle weakness, and/or spastic contractions of the muscles involved in respiration [9, 92]. Lesions in the thoracic segments of the spinal cord are also related to respiratory complications. In 2005, Cotton and coworkers [93] conducted an investigation to determine the respiratory complications and mortality risk associated with thoracic spinal cord injury. They found that 51% of high thoracic (T_1–T_6) and 28% of T_7–T_{12} spinal cord-injured individuals suffer serious respiratory complications such as pneumonia and recurrent respiratory infections. Individuals with either cervical or thoracic SCI are at risk of developing respiratory insufficiency due to total or partial paralysis of the muscles involved in breathing.

Another clinically relevant aspect of impaired respiration in individuals with SCI is the inability to cough adequately probably caused by weakness of the abdominal muscles. Neurophysiologically, the cough has been described as a phenomenon initiated from structures innervated by the vagus cranial nerve. Afferent fibers from rapid-adapting receptors run within the vagus nerve. When stimulated, these receptors are responsible for initiating the cough reflex [15]. Vagal fibers bypass the spinal cord and therefore should not be affected by SCI, even in complete cervical lesions. In fact, cough reflex is preserved in cervical and upper thoracic SCI. However, these individuals suffer from ineffective coughing [15] resulting in accumulation of secretions that can cause airway obstruction and provide growth media for the development of pneumonia [93].

Injuries to the cervical segments of the spinal cord often result in paralysis of the respiratory muscles [88]. Complete cervical injuries above the level of phrenic motoneurons may cause paralysis of the muscles of both inspiration and expiration, leaving the individual mechanical ventilator-dependent. High cervical incomplete (C_2–C_4) or cervical lesions below C_5 (C_5–C_8) are likely to produce paralysis, weakness, or spasticity in the muscles used to perform forced respiration. In these individuals, neural control of the diaphragm is preserved, and inspiration can occur independently [14]. Independent breathing may occur even with a partially paralyzed diaphragm as was demonstrated in animal studies [94]. Studies performed in canines demonstrated that with unilateral phrenic nerve transection, the partially paralyzed diaphragm can be compensated for by the nonparalyzed contralateral hemidiaphragm and by the intercostal muscles [94].

In addition to paralysis, muscle weakness is another feature frequently observed in spinal cord-injured individuals. Weakness after SCI has been observed in the limbs [95] and abdominal muscles [96]. Although muscle weakness of the respiratory muscles has not been intensely studied, others have suggested that it is related to the paradoxal breathing in individuals with SCI [97]. This occurs when, in contrast to uninjured individuals, the upper anterior rib cage moves inward during inspiration in persons with cervical or high thoracic SCI [98]. This inappropriate rib-cage movement is the result of a lack of spinal motor activation of the external intercostals combined with the excessive compliance of the abdominal wall due to weak muscle contraction [97]. This abnormal breathing pattern is more frequent in cervical than thoracic SCI; however, it does not occur uniformly across all cervical spinal cord-injured individuals [99–102]. This phenomenon depends on rib cage

elasticity and on the activity of the accessory muscles for inspiration. When EMG recording from scalenes is silent during inspiration, this paradoxal movement of the rib cage is consistently present [99]. Therefore, abnormalities in respiration mechanics are related to abnormal neuromuscular activity including paralysis, muscle weakness, and spasticity.

As is commonly seen in limb muscles [103], unintended contractions and continuous activation can occur in the muscles of respiration [69]. These spastic contractions of the abdominal muscles impose a substantial load on inspiratory muscles, causing an imbalance between the respiratory load and the capacity of the inspiratory muscles to carry that load. Laffont and coworkers [9] conducted an investigation in a C_4 AIS A SCI individual in which EMG activity of the abdominal muscles was simultaneously recorded with pulmonary air flow esophageal pressure, gastric, transdiaphragmatic pressure, and spirometrical parameters. They found that in spite of the diaphragmatic weakness, the patient did not suffer breathlessness episodes unless spastic contractions of the abdominal muscles occurred. Transient spastic contractions of the abdominal muscles were associated with significant increases in gastric and esophageal pressures. This additional pressure must be overcome for inspiration to occur, imposing a considerable load on the inspiratory muscles resulting in dyspnea.

In 1997, Roth and coworkers [92] conducted an investigation to determine whether ventilatory dysfunction was related to the level of injury and spasticity by testing pulmonary function and correlating spirometrical values with spasticity scores obtained using the Ashworth scale in humans after SCI. The Ashworth scale is a subjective method used to assess spasticity in which the examiner rates the amount of muscle tone (spasticity) felt as a limb is moved passively through its arc of motion [104–106]. They found that the level of the injury is correlated with respiratory variables, but no correlation was found between pulmonary function and limb spasticity [92]. The key limitation of their study was that the Ashworth scale was not designed to evaluate trunk spasticity.

Therapies to Restore Respiratory Function After Spinal Cord Injury

The standard of care for respiratory function management in patients with non-ventilator-dependent SCI is to respond to emergent pulmonary complications such as infections that can develop [107], and none of the rehabilitative modalities have yet been proven to be clinically effective [108]. However, there are many potential strategies for preventing respiratory failure in individuals with SCI. Some are intended to compensate for weak muscle control such as positive-pressure ventilation and mechanically assisted coughing [109]. Abdominal strapping with a nonelastic binder that is applied around the abdomen is used in order to prevent the paradoxical expansion of the abdomen that is common in cervical SCI [110]. This technique has been shown to improve forced expiration and coughing in patients with paralyzed or weak abdominal muscles. Conversely, several studies have demonstrated that abdominal strapping has minimal effects in improving forced expiration at rest [88, 110, 111] or during exercise [112].

Exercise has, in general, been shown to increase fitness and improve the ventilatory function of individuals with acute [113] and chronic SCI [114]. Physical capacity is significantly decreased in people with cervical or thoracic SCI due to paralysis of the muscles below the level of the injury, altered autonomic control, and inactivity [115]. It has been shown that exercise in individuals with chronic SCI elicits a metabolic response characterized by increases in oxygen consumption, minute ventilation, and heart rate [116, 117]. In addition to these general factors involved in increasing respiratory activity, exercise-related effects are associated with the excitation of cerebral cortex, limbic and reticular activating systems, hypothalamus, and central chemoreceptors [118]. Specifically, strength training of the

pectoralis major in complete lower cervical cord-injured individuals significantly improved expiratory function by significantly increasing expiratory reserve volume and decreasing residual volume [22]. Locomotor training, an activity-based therapy for gait rehabilitation, has also been shown to increase oxygen consumption, heart rate, and pulmonary ventilation) [117].

Respiratory neuroplasticity, defined as a persistent morphological and functional change in neural control based on prior experience [119], is critically dependent on the establishment of necessary preconditions, the stimulus paradigm, balance between opposing modulatory systems, age, gender, and genetics. Respiratory plasticity can be induced by hypoxia, hypercapnia, exercise, injury itself, stress, and other interventions [119, 120]. Recently, an intermittent hypoxia has received considerable experimental emphasis as another restorative modality in animal [121] and human models [122, 123]. This approach, known as long-term facilitation (LTF), is based on physiological mechanisms associated with ability of spinal circuitry to learn how previous repeated hypoxic bouts affect breathing by adjusting synaptic strength between respiratory neurons. Although chemical feedback, such as hypoxia, initiates LTF, it is unknown whether natural modulation of mechanical feedback (from vagal inputs) also causes motor plasticity [122].

Training designed to specifically target and activate respiratory muscles has been successful at improving inspiratory and expiratory pressures, total lung capacity, peak oxygen consumption, and 1-min ventilation by inducing central neural remodeling through the processes of activity-dependent plasticity [124] in patients with restrictive thoracic disease [125] and in acute and chronic spinal cord-injured individuals [87]. Respiratory muscle training can be performed in two modalities: inspiratory muscle strength training and expiratory muscle strength training. Inspiratory muscle training has been widely recommended as an effective respiratory therapy for subjects with chronic obstructive pulmonary disease [126]. Expiratory muscle training has been found to bring significant improvement to expiratory muscle strength, pulmonary function, and coughing in patients with restrictive thoracic disease [124] and SCI [87].

Functional electrical stimulation applied over the muscles of expiration can improve respiratory function and cough effectiveness [91, 127, 128]. Direct electrical stimulation of the phrenic nerve has been used to produce inspiration in the USA, Finland, and Austria as an alternative to the mechanical ventilator [129, 130] for individuals with a paralyzed diaphragm. However, this approach is proving less successful than diaphragm pacing [131–133]. In addition, DiMarco and Kowalski evaluated a novel method of inspiratory muscle activation, which involves the application of high-frequency (>200 Hz) stimulation to the ventral surface of the spinal cord in the high thoracic region in animal model [134].

Lin and colleagues [135–137] conducted a series of investigations to determine the effectiveness of functional magnetic stimulation as a method for restoring maximal expiratory pressure with the associated restoration of cough. They located the coil along the lower thoracic spine (between spinal processes T_6–T_{12}) to stimulate expiratory muscles and produced increasing maximal expiratory pressure, as well as forced expiratory flow [138]. In addition, after a 4-week functional magnetic stimulation expiratory muscle training in spinal cord-injured individuals, values of maximal expiratory pressure and forced expiratory flow at total lung capacity and at functional residual capacity were shown to be significantly increased. The most relevant finding was that functional magnetic stimulation significantly improves expiratory muscle strength, indicating that this method can be used as a noninvasive therapeutic technology in respiratory muscle training for persons with SCI [136].

Summary

The injury to the spinal cord is commonly associated with respiratory muscle paresis, paralysis, and spasticity resulting in pulmonary dysfunctions that impact the quality of life and are listed among the leading causes of death in SCI population. Progress is being made in the treatment of respiratory dysfunction brought by SCI, and evaluation of any new intervention requires the use of appropriate objective outcome measures. Although none of the rehabilitative techniques for the restoration of respiratory motor control in patients with chronic SCI have yet been proven to be effective, it is a hope and expectation that the results of many ongoing studies will support the application of physiologically based rehabilitation strategies to manage these conditions as the standard of care in the future.

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Table 1

Actions and innervation of the inspiratory muscles (diaphragm, external intercostals, scalenes, sternocleidomastoid, upper trapezious, and parasternal part of the internal intercostals) and expiratory muscles (internal intercostals, rectus abdominus, obliques, pectoralis, and latissimus dorsi)

Muscle	Quiet inspiration	Forced inspiration	Quiet expiration	Forced expiration	Cough	Innervation	Action
Diaphragm	√	√			√	Phrenic nerve (C3–C5)	Descends enlarging thoracic cavity
External intercostals	√	√			√	Intercostal nerve (T2–T6)	Elevation of the ribs
Scalenes		√			√	Spinal nerves C2–C7	Elevation of the 1st rib
Sternocleidomastoid		√			√	Cranial nerve XI (accessory nerve)	Elevation of the upper ribs and sternun
Upper trapezious		√			√	Cranial nerve XI (accessory nerve)	Elevation of the ribs
Internal intercostals	√[a]	√		√	√	Spinal nerves T1–T6	Reduce thoracic cavity
Rectus abdominus				√	√	Spinal nerves T5–L1	Reduce thoracic cavity
External obliques				√	√	Lower 6 intercostal nerves and subcostal nerve	Reduce thoracic cavity
Internal obliques				√	√	Lower 6 intercostal nerves and subcostal nerve	Reduce thoracic cavity
Pectoralis major (clavicular portion)				√		Spinal nerves C5–C7	Reduce thoracic cavity
Latissimus dorsi				√		Spinal nerves C6–C8	Reduce thoracic cavity

[a] Parasternal part of the internal intercostals