Vilnius University

FACULTY OF MEDICINE

Department of Rehabilitation, Physical and Sports Medicine

Hosam Aldeen Gharedah, 6th Year, Group 3

INTEGRATED STUDY MASTER'S THESIS

Respiratory Function and Therapy after Spinal Cord Injury in Cervical Level (Tetraplegia)

Supervisor: Lect. Jurate Kesiene

Head of the department: Dr. Tomas Aukštikalnis

Vilnius 2025

Aldeen.gharedah@mf.stud.vu.lt

Table of Contents

Table of figures

Table of tables

Table 4	Summary of respiratory exercise interventions
Table 5	Summary of respiratory phases after cervical spinal cord injury

1. List of Abbreviations

Abbreviation	Full term
AIH	Acute intermittent hypoxia
ASIA	American Spinal Injury Association
BDNF	Brain-derived neurotrophic factor
BiBAP	Bilevel positive airway pressure
CMAP	Compound muscle action potential
CPAP	Continuous positive airway pressure
CSci	Cervical spinal cord injury
CSPG	Chondroitin sulphate proteoglycan
EMG	Electromyography
FES	Functional electrical stimulation
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IL-6	Interleukin-6
FEV1	Forced expiratory volume in 1 second
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
CPAP	Continuous positive airway pressure
BiBAP	Bilevel positive airway pressure
TNF-a	Tumour necrosis factor-alpha
IL-6	Interleukin-6
IMT	Inspiratory muscle training
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
MVV	Maximal voluntary ventilation

NIV	Non-invasive ventilation
PNS	Phrenic nerve stimulation
SCI	Spinal cord injury
SDB	Sleep-disordered breathing
TESCoN	Transcutaneous electrical spinal cord neuromodulation
TNF-α	Tumour necrosis factor-alpha
VNS	Vagus nerve stimulation

2. Summary

Cervical spinal cord injury (CSci) is a drastic neurological condition that causes impairment in the autonomic nervous system in the motor and sensory level. The most common complication which is a life-threatening in (CSci) or tetraplegia patient takes place in the respiratory system and the reason behind is the loss of voluntary control of both accessory muscles and diaphragm, this dysfunctions results in decline in the lungs capacity, inability to cough properly and inadequate ability to clear the mucous in the airways efficiently, as well as, the accumulation of these secretions, these issues will lead to respiratory complications in the respiratory system such as pulmonary infections, atelectasis and other sleep-disordered breathing.

This thesis will go through the mechanisms underlying respiratory disfunction in cervical spinal cord injuries patients and will concentrate on complications, pathophysiology, therapeutic interventions and combine those interventions if needed. Some of those issues discussed in this study were Pneumonia, atelectasis and sleep disorders. It will explain risk factors, diagnostic approaches and treatments strategies. Studies have addressed that respiratory muscle training enhances pulmonary function, specifically in subacute and chronic injury phases, additionally, game-based respiratory rehabilitation devices and tools have demonstrated a huge gain by promoting engagement, inspiratory and expiratory strength and improvement of physiological well-being state overall. Innovative procedures such as transcutaneous electrical spinal cord neuromodulation (TESCon) have demonstrated effective result and outcomes regarding voluntary breathing and cough capability. This literature review will highlight effective rehabilitation strategies by reviewing current literature and recent advances in this regard which can improve respiratory function and improve the

overall quality of life if tetraplegia populations. It will give a solid view about the early intervention role to prevent unpleasant long-term complication.

3. Keywords:

Cervical spinal cord injury, Tetraplegia, Respiratory dysfunction, Neuroplasticity, Respiratory therapy, Functional electrical stimulation (FES), Pulmonary complications in cervical spinal cord injury, Non-invasive neuromodulation; Respiratory muscle training; Spinal rehabilitation.

4. Introduction

Spinal cord injury (SCI) is a massive condition which cause disability in sensory or motor autonomic system and can be permanent disruption. among those conditions comes the cervical spinal cord injury (CSci) which results in tetraplegia, being among the most severe injuries, often causing significant autonomic dysfunction, CSci is categorized into three clinical phases acute (within 14 days of injury), subacute (2-8 weeks after the injury) and chronic (almost more than 8 weeks). Each year, between 250,000 and 500,000 people worldwide suffer from SCIs, mainly after traffic accidents, falls, and sports, leading to a massive disability in these individuals and make them more dependent on medical care. These cases of (CSci) injuries are more prone to respiratory-related hospitalisations, particularly due to pneumonia, which is a major cause of death in the first year following the injury(1). The condition affects the upper and lower limb along with the autonomic systems, and the respiratory system which is one of leading cause of morbidity and mortality in individuals with CSci(2). Respiratory disruptions start from the interruption of the neural pathways that govern the respiratory muscles, prominently the phrenic nerve, which is crucial for diaphragm function, often compromised in severe cervical spinal cord injuries. This leads to hypoventilation and increases the risk of respiratory infections and complications (1). Damaging to the respiratory function in CSci individuals happens due to the impairment of descending neural pathway that controls the diaphragm, intercostal muscles and accessory muscles of respiration(3). This impairment in the respiratory system takes place due to the impairment of the neural pathways between the respiratory centre which exists in the medulla oblongata and pons, and motor neurons supplying respiratory muscles exist within the cervical level of the spinal cord (C3-C5) for diaphragm, (T1-T12) for the intercostal muscles (3). This impairment will lead to significant respiratory disfunction, inability to clear mucous properly, increasing infections, and decreasing lunges capacity leading in severe cases to life-threatening condition such as pneumonia(4). Recent studies show a huge advantage when it comes to some strategies and therapeutic methods to improve the quality of life of those individuals. These techniques involved intermittent hypoxia therapy (AIH), functional electrical stimulation (FES) and vagus nerve stimulation (VNS) who were among most popular techniques used to improve respiratory muscle functions(5). They work on the improvement of motor function via anti-inflammatory effects and promote neuroplasticity(3). AIH enhances neural plasticity and recovery of respiratory and non-respiratory motor functions after SCI by stimulating serotonergic neurones, enhancing the expression of brain-derived neurotrophic factor (BDNF) in spinal motor pathways(4). This thesis will explore the mechanisms of respiratory dysfunction after CSci and go through various of treatment options of respiratory issues. It will focus on the integration of these alternatives into clinical practice and overall patient care. It will go through pathophysiology of respiratory dysfunction in cervical spinal cord injury, all possible therapeutic intervention, as well as, combining some treatment strategies for highest respiratory muscle improvement potential. The aim of this study is to estimate the dysfunction of respiratory system, and all possible interventions post cervical spinal cord injuries. It will highlight the contrast among different study opinions about mechanisms who have been utilised and studied and will include some of the clinical application of invasive and non-invasive management. This literature review will go through and compare different literatures on respiratory pathophysiology in CSci, while estimate several respiratory procedures based on their results and methodologies, additionally, assessing the quality of the outcomes while integrating several strategies and interventions in the practices to add up extra advantages.

5. Strategies and methodology:

This thesis is a comprehensive literature review about respirator functions after cervical spinal cord injury (CSci) in the cervical level, it analyses pathophysiology, possible respiratory complication, interventions, combined treatments by reviewing research articles. The aim of this literature review was to assess risks such as pulmonary infections and ventilator dependency after the injury and evaluate both traditional and advanced rehabilitation strategies including neuroplasticity-based therapies used to restore respiratory independence. It has primarily used databases such as science direct, PubMed, and google scholar, Furthermore, in this thesis articles and studies included which has been published within 15 years. To collect research articles, I have used key terms such as "Respiratory dysfunction in cervical spinal cord injury CSci", "Inspiratory muscle training in tetraplegia population”, "Acute intermittent hypoxia (AIH) in CSci, "Functional electrical stimulation (FES) after cervical spinal cord injury, "vagus nerve stimulation after CSci (VNS)", "Neuroplasticity in tetraplegia individuals", "pulmonary complications after CSci", "pneumonia following cervical spinal cord injuries".

Only English language articles published between 2000 and 2025 were included to preserve the relevance. These articles were chosen after reading their titles and abstracts at the beginning. Studies focusing on respiratory impairment, therapies, or rehabilitation strategies after cervical spinal cord injuries CSci. As a narrative review, this study may lack subjective nature of study selection, but at the same time, every effort was included to weigh the range of evidence incorporating crucial and vital perspectives from all literatures.

Peer-articles who have been published between 2000 and 2025, and the English language was only language used to write this thesis. All research and advances concentrated Mainly on cervical spinal cord injuries therapies, pathophysiology, pulmonary complications and managements of respiratory system post injuries.

Non-English research and studies were excluded from this literature review and all publications about lumbar or thoracic injury regions of spinal cord were also filtered out. Articles without respiratory dysfunction focus were ignored as it was not completely relative to this thesis. Additionally, no Case reports without adequate findings were included.

The initial search accumulates 70 articles, after reading their titles and abstracts, 35 articles were excluded for not aligning with the inclusion criteria. 9 articles were excluded because of their partial irrelevance, and finally, 26 articles were included in this final literature review.

6. Background

6.1 The epidemiology and the influence of spinal cord injury

Tetraplegia or cervical spinal cord injury CSci counted for up to 60% of total percentage of all spinal cord injuries and is almost among joint population due to vehicle accidents trauma and falls, as well as sport injuries(6). With the most affected levels being between C4 to C6, this level will result in tetraplegia and autonomic instability making the respiratory consequences the main cause of mortality in these populations(4). Both sensory and motor neurons in respiratory system will be affected after CSci. Disruption to the descending pathways will lead to the impairment in diaphragm through phrenic nerve disfunction between (C3-C5), intercostal and abdominal muscles impairment between (T1-T12). This impairment will lead to ineffective cough, accumulation of the secretion and further decline in the lung(6). Cervical spinal cord injury (CSCI) has a profound impact on respiratory function, often leading to hypoventilation, ineffective coughing, and increased risk of pulmonary infections such as pneumonia. These complications are a major cause of mortality in tetraplegic patients. The injury also results in long-term disability and dependence on ventilatory support, especially in high-level lesions of the cervical spine. Beyond clinical effects, CSci imposes a significant socioeconomic burden due to the high cost of acute care, rehabilitation, and lifelong support needs. It primarily affects young males and places strain on healthcare systems. Outcomes are further influenced by external factors like delayed rehabilitation, hospital practices, and physician decisions. This will emphasize the need for early integrated respiratory and rehabilitative care. Weak cough reflex increase vulnerability to infections such as pneumonia which is the major causes of death in tetraplegic patients. High-level injuries often result in chronic disability and dependence on respiratory aids. The injury also presents a major socioeconomic issue due to the expenses of medical treatment, rehabilitation, and ongoing support, especially for the young males which are most often affected. Systemic issues like delayed rehab and hospital policies further affect patient outcomes highlighting the importance of integrated early intervention in respiratory and rehab care. Those physiological problems will result in more potential risk of atelectasis, pneumonia and chronic respiratory insufficiency. While some authors concentrate mainly on muscles dysfunction as the main risk factor for mortality in these individuals, others were pointing out the importance of modifiable external factors such as delayed access to rehabilitation and mechanical ventilation dependency or hospital acquired infections as being more involved. For example, Luo et al. emphasized age, smoking history, and prolonged surgical time as major predictors of pulmonary infection, alongside the level of injury(4), in the other hand, Jian and Zhang’s study highlighted a non-linear dose-response relationship between age and the need for tracheostomy, suggesting that clinical decisions may be influenced more by physician judgment and hospital practices than by injury severity alone(7).

Tetraplegia patients cause a huge problem at the socioeconomic level as it requires a massive resource due to the permanent disability. These patients who experience this injury in the cervical level specifically in the first year and are at the highest risk for the respiratory complications and ventilatory failure (9). Males under age 30 remain at highest risk for traumatic SCI, with regional spikes in prevalence depending on access to trauma systems(2). The rehabilitation creates substantial socioeconomic burden due to the permanent loss of motor and autonomic function, especially when the injury occurs at the upper cervical level of the spinal cord. The leading cause of death in Tetraplegia patients are mainly due the complications related to respiratory system and rises more focus on promising therapeutic interventions(5). The higher risk of respiratory complications including pneumonia created an extra effort and pressure for researcher to go in depth in all promising therapeutic interventions, combining procedure and utilising several mechanisms as a combination to decrease the need for mechanical ventilators and improve the quality of life for these individuals overall(8).

After the incident of cervical spinal cord injury (CSci), an impairment will take place in neural pathway that controls voluntary and autonomic breathing muscles. Injuries which happen between spinal segments C3 and C5 will impair the phrenic nerve which innervate the diaphragm and can lead to a real problem in respiratory function. These disruptions manifest as hypoventilation, inability to cough normally and consequently pulmonary infections(6). Some advances highlighted the role of intercostal and abdominal muscles (T1-T12) in the forced expiration and cough reflex generation, and when these muscles denervated, it will lead to lungs collapse(8). While newer advances suggest that the rib cage motion, in patients with partial muscle paralysis offering more promising compensatory mechanism in partial injuries(3). Gonzalez-Rothi and colleagues highlighted the role of spinal interneurons and pre-phrenic circuits which might maintain some neuronal activities even after high-level injury. For example, intermittent hypoxia or spinal stimulation-sub lesional plasticity may help in breathing adequately(3). However, this perspective wasn’t completely acceptable as some researchers suggested that the extent of plasticity is overestimated during animal models and may not be transitioned equally into chronic human SCI. Hormigo et al suggested, while induced plasticity is a fact, its clinical relevance stay limited without complete targeted intervention over time(2). The literature aligns with two different schools: one confirms the potential of recovery of respiratory motor impairment via the maintenance of neural pathways and plasticity-based interventions. While the other school underestimated the permanence of respiratory motor disruption and align more for the long-term need for ventilatory support in most CSci patients, particularly in individuals with the injury take place at the highest level of cervical spinal cord region. Different procedures have been evolved to manage the consequences following cervical spinal cord injuries. These interventions range from preserved managements such as inspiratory muscle training (IMT), to more advanced approaches Such as acute intermittent hypoxia (AIH), functional electrical stimulation FES and vagus nerve stimulation (VNS), but still studies offered diverging opinions regarding their efficacy and the duration of managements and benefits, as well as their clinical applications. Recent advances have clearly shown that the best outcomes were by combining therapies, for example, pairing (AIH) with task-specific training has led to the more efficient upper limb function particularly with incomplete CSci(9), at the same time, integration of (FES) with the respiratory training played a huge role in ventilatory tolerance and led to less frequent infections. This thesis aimed to clearly explain mechanisms behind respiratory dysfunction after cervical spinal cord injury, evaluates invasive and non-invasive procedures, as well as describes best outcomes of respiratory recovery strategies, particularly, when therapies were combined in a proper effective way.

7. Physiology of Respiratory system

Breathing Mechanisms and Respiratory Muscles are Controlled by Central neural pathways in the brainstem, particularly within the dorsal and ventral groups in the medulla. That set the respiratory rhythm and mobilise the muscles who are crucial for air movement facilitating normal breathing and gas exchange(6). (T1-T12) innervate the intercostal muscles which expand and make the rib cages more stable in the inspiration process. Signals from these groups travel down the spinal cord activating the motor neurone that control respiratory muscles [Fig 1], including the diaphragm, intercostal muscles, and abdominal muscles(10). The phrenic nerve travelling from C3-C5 segment innervating the diaphragm which is the most important muscle for breathing adequately particularly the inspiration phase. Its contraction is crucial for lung air intake, ensuring adequate tidal volume and gas exchange. Additionally, the accessory muscles help in forcing expiration and coughing and are innervated by the spinal nerves in the lumbar and lower thoracic region(1). These muscles play a vital role in airways clearance and respiratory compensation when there are uncommon physical activities or when there are some pathological issues in the body.

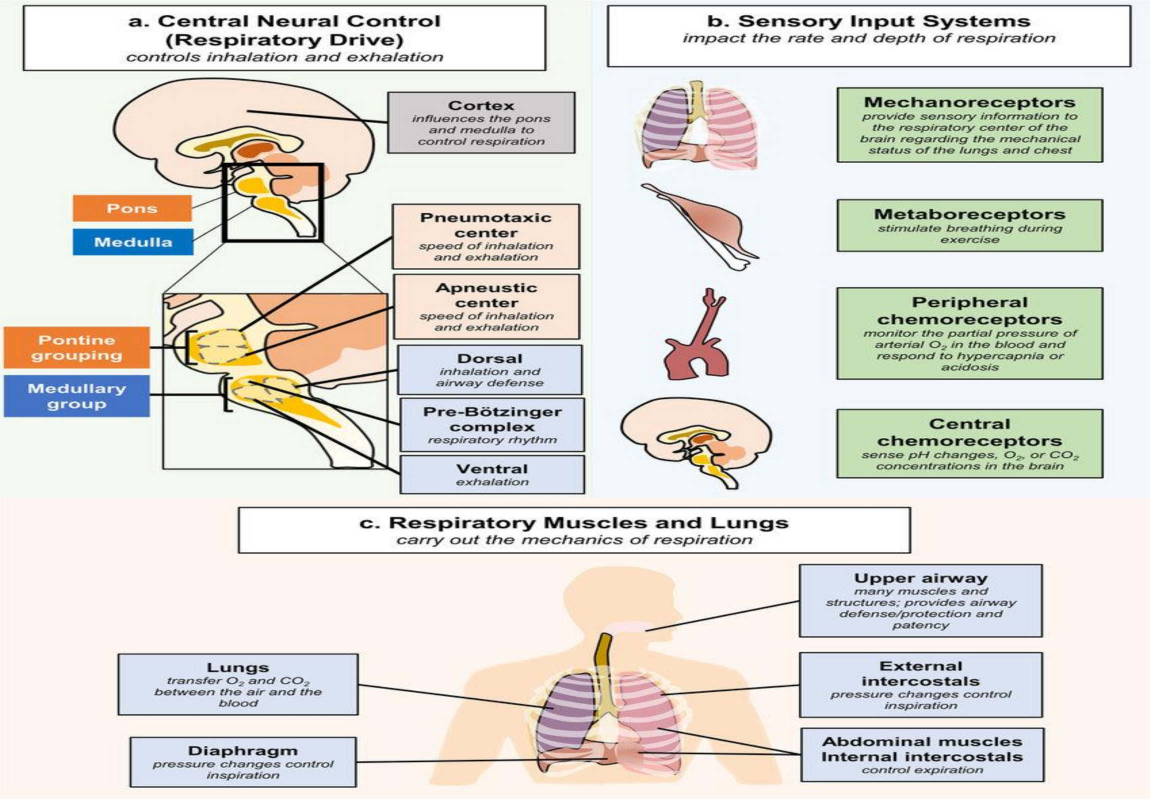

Fig 1 Respiratory neural control pathways.

Diagram shows brainstem and spinal cord connections to respiratory muscles via the vagus and phrenic nerves. Efferent and afferent pathways coordinate diaphragm, intercostal, and abdominal muscle function, with cholinergic signaling indicated at neuromuscular junctions. Webster LR, Karan S. The physiology and maintenance of respiration: a narrative review. Pain Ther [Internet]. 2020;9(2):467–86. Available from: https://www.researchgate.net/publication/345322590_The_Physiology_and_Maintenance_of_Respiration_A_Narrative_Review [cited 2025 May 3].(11)

8. Anatomy of cervical spinal cord region

The spinal cord is essential in controlling breathing by linking to respiratory muscles through spinal nerves, The phrenic nerve stems from the C3-C5 spinal segments is responsible for activating the diaphragm, the chief muscle for breathing. This setup exposes the diaphragm to a huge risk from severe cervical spinal cord accidents. Injuries at or above the C3 segment could result in a complete paralysis of the diaphragm, leading to the requirement for lifelong mechanical breathing support, while injuries below C5 typically save some diaphragmatic functions but impair critical muscles necessary for effective coughing and forceful expiration(1,10).

9. Anatomy of respiratory system:

Breathing is a procedure where a complicated physiological process happens, the lungs, airways and neural connections [Fig2] communicate for ventilation and gas exchange, which are very crucial for managing breathing procedure. This process begins when the diaphragm acts by creating a difference in pressure to intake the air insides the lungs by contracting and expanding the thoracic (negative intrathoracic pressure). This expansion is supported by the lifting of ribs by the external intercostal muscles. All these muscles contribute to the respiration process and are called muscles of respiration [Table 1]. During higher respiratory demands, other muscles like the sternocleidomastoid and scalenus are recruited to support deeper inhalation(1,10).

Table 1. Respiratory Muscles and Their Innervation in Cervical SCI, (Adapted from Galeiras Vázquez et al. [1] Galeiras Vázquez R, Rascado Sedes P, Mourelo Fariña M, Montoto Marqués A, Ferreiro Velasco ME. Respiratory management in the patient with spinal cord injury. Biomed Res Int. 2013;2013:168757. (12)

Muscle group	**Function**	**Innervation**	**Affected in CSci**
Diaphragm	Inspiration	C3-C5	Yes
Intercostal muscles	Chest expansion and stability	T1-T11	Partially affected
Abdominal muscles	Forced expiration and coughing	T6-L1	Yes
Accessory muscles	Deep inspiration	C1-C4	May compensate in incomplete injury

10. General Pathophysiology of Spinal Cord Injury (SCI)

Spinal cord injuries (SCI) happens when the trauma hits the spinal cord, it leads to several issues and deficits in the neurological level, initially, the accident whether it is a contusion or compression or other trauma will damages the spinal cord structure affecting axons, cell membranes and blood vessels which triggers secondary issues such as vascular disfunction, glutamate induced toxicity and impaired blood flow, as well as, apoptosis [Fig2]. Those secondary issues affect motor, sensory, autonomic and respiratory functions. When the trauma hits the cervical spine, it will lead to long term neurological deficit in cervical region due to impairment of neural pathways involving diaphragm and intercostal muscle control(1). This will trigger a series of cellular and molecular events such as: Ischemia and hypoxia due to disruption of blood flow, and excitotoxicity because of intensive glutamate release, as well as infiltration of immune cells and pro-inflammatory cytokine release. Additionally, it will lead to dysfunction of mitochondria and oxidative stress. As the cervical spine includes vital motor pathways that innervates the diaphragm via the phrenic nerve and intercostal muscles, as well as the accessory muscles of respiration. so, this damage will in turn lead to respiratory insufficiency, and inability to get rid of mucous normally causes accumulation of secretions, and finally more risks for infections who are the leading cause of mortality in this population(4). Understanding this mechanism will help in determination of the right neuroprotective strategies, and early interventions, additionally, stabilising the injury by supporting recovery of the respiratory and autonomic Functions.

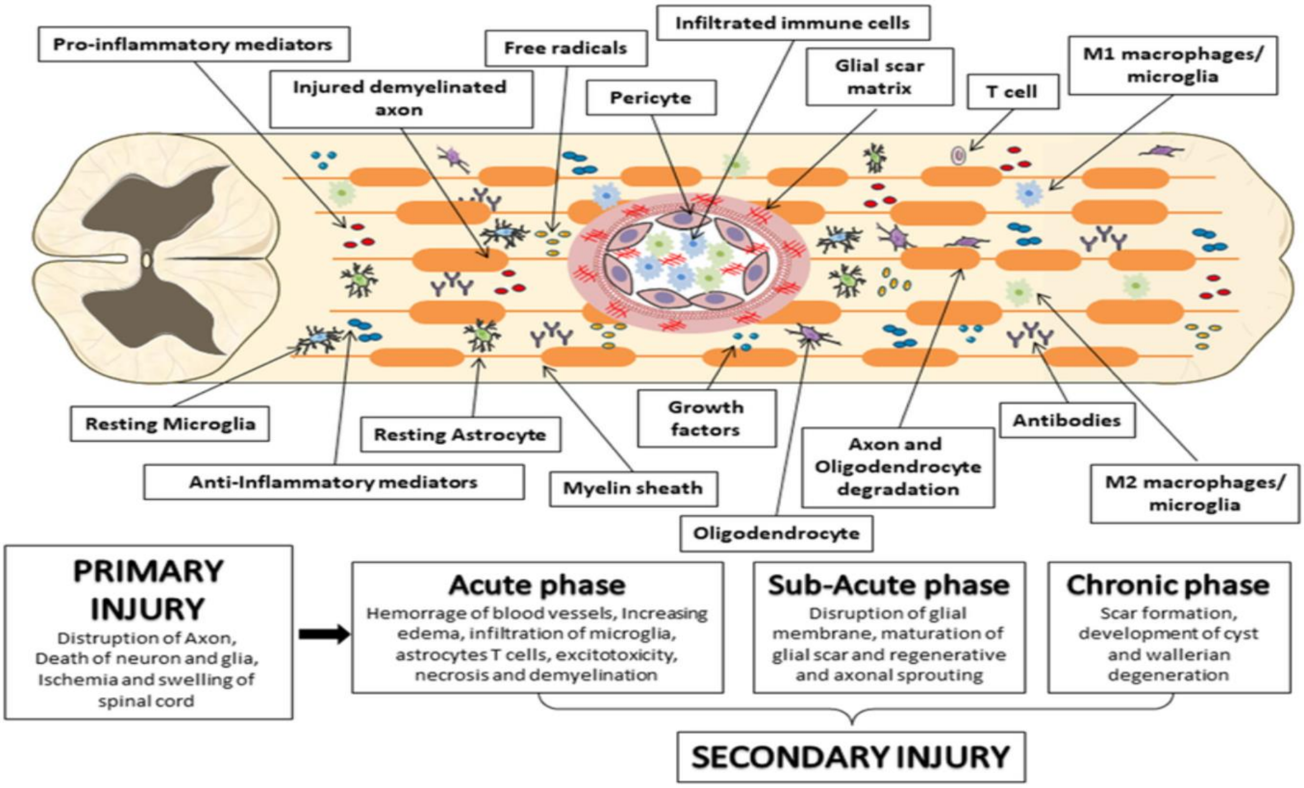

Fig 2**.** Pathological cascade following spinal cord injury.

Illustration of primary injury and secondary injury phases (acute, sub-acute, and chronic), highlighting cellular and molecular changes such as inflammation, demyelination, immune cell infiltration, and scar formation. An Overview of Spinal Cord Injury Experimental Studies - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Pathophysiology-of-spinal-cord-injury-SCI-This-schematic-diagram-illustrates-the-phase_fig2_367139046 [accessed 15 Apr 2025](13)

11. Pathophysiology of Respiratory Dysfunction in Cervical Spinal Cord Injury

The impairment of the descending neural pathway in tetraplegia individuals which controls the respiratory muscles [Fig 3], the intercostal muscles, diaphragm and all accessory muscles are the main reason for respiratory dysfunction in tetraplegia patients as well as, the phrenic nerve C3-C5 which is the main nerve which innervates the diaphragm is the most exposed to this injury and in turn causes the lungs to decline in their capacity, as well as, the inability to cough normally(2). These cascades of events [Fig 6] such as inflammation, excitotoxicity, and neural apoptosis lead to more decline in the respiratory functions and reduction in neuroplasticity, so, any decline in compensatory mechanism will for sure happens due to the exacerbation of mid cervical interneuron post cervical spinal cord injury which coordinates the breathing according to the literature(3). While any damage to the thoracic spinal segments (T1–T12) impair the intercostal muscles, which are essential for chest wall expansion leading to reduced lung volumes. Furthermore, the abdominal and accessory muscles impairment will worsen the patient's ability to clear airways secretions which is severely compromised, raising the risk for mucus plugging, atelectasis, and lungs infections(1). Impairment on the cellular level will cause disruption in neural plasticity and decrease the chance for functional recovery. While some advances suggested that this kind of injuries also affect the med-cervical interneurons, which help coordinate rhythmic breathing pattern, and any problem in this area will reduce the compensatory mechanism leading the respiratory system to lose its stability(9).

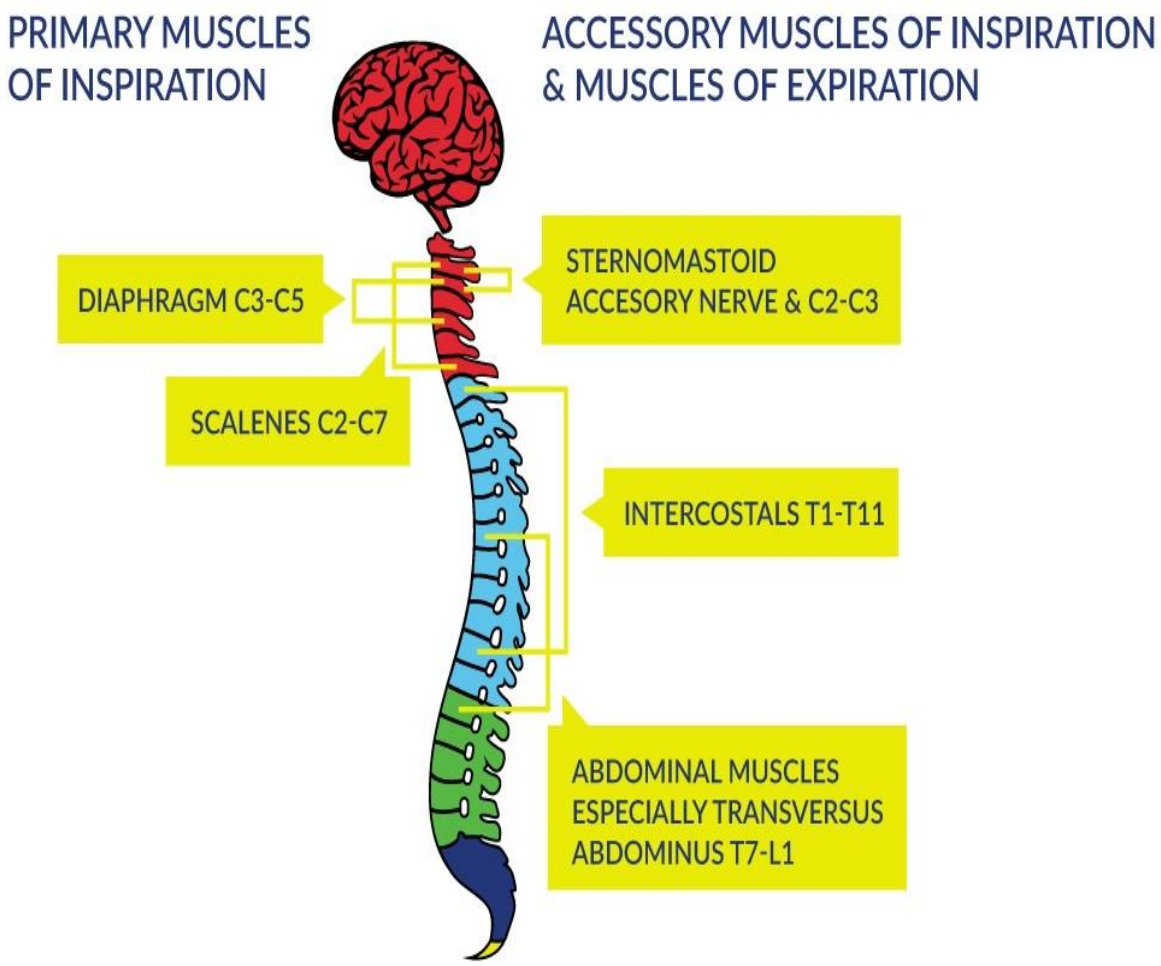

Fig 3. Innervation of respiratory muscles and the effects of spinal cord injury. The diagram depicts how injuries at different spinal levels impact specific respiratory muscles, contributing to respiratory dysfunction. Spinal Cord Injury Rehabilitation Evidence (SCIRE) [cited 2025 May 3]. Available from: https://scireproject.com/evidence/respiratory-management-rehab-phase/introduction/(14)

The brainstem controls the respiration by sending signals through descending pathways to the phrenic nerve C3-C5 that innervates the diaphragm [Fig 4]. Which is the leading muscle for inspiration, as well as the additional respiratory muscles and the intercostal muscles who get their signals from thoracic spinal cord helping in expansion and expiration(2). Following the initial trauma a cascade of secondary pathological conditions will exacerbate respiratory issues. These disruptions include neuroinflammation, demyelination, oedema of the spinal cord, and loss of interneurons in the cervical segments. These interneurons are crucial for controlling respiratory muscles, and any damage to them will leads to potential damage to phrenic motor neurone and the networks they interact with, markedly diminishing the prospects for spontaneous respiratory recovery or effective neuroplastic changes(3). A significant outcome of secondary damage is the stiffening of the chest wall and muscle spasticity over time. Starting with flaccid paralysis (spinal shock), the evolving condition brings up muscle contractures and diminished chest wall flexibility which restrict ventilatory mechanics and lung expansion. This restriction worsens restrictive lung patterns leading to chronic hypoventilation that typically requires long-term ventilatory support(1). Moreover, autonomic dysfunction following CSci, particularly with high cervical injuries resulting in parasympathetic overactivity. This results in increased bronchial secretions, bronchospasm and reduced mucous clearance. These effects collectively increase the likelihood of developing atelectasis, mucus plugging, and pneumonia in the period following the injury(10). Another problem is the decrease of the lung's capacity caused primarily by the loss of intercostal and accessories muscles activation, this reduction and inability to clear the mucus properly will end up in the tendency for more infections risks and complications(5).

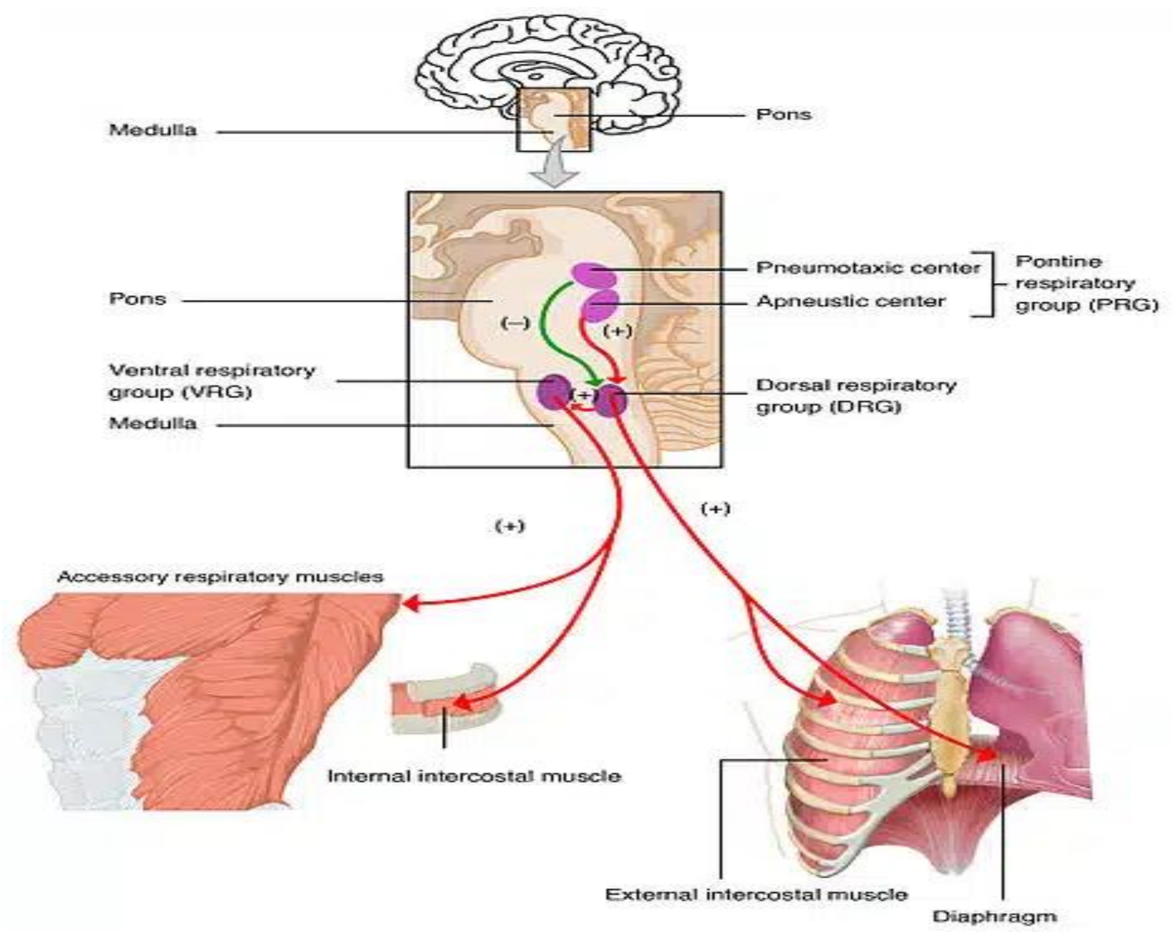

Fig 4**.** Neural pathways control respiration.
Diagram shows brainstem projections to phrenic and intercostal motor neurons and how cervical SCI may disrupt these connections.

TeachMe Physiology. Neural Control of Ventilation [Internet]. [cited 2025 May 3]. Available from: https://teachmephysiology.com/respiratory-system/regulation/neural-control-ventilation/(15)

When the loss of motor neurones that control the respiratory muscles occurs, the mechanism of secondary injury will exacerbate the respiratory system causing respiratory dysfunction. One of the most immediate disruptions is hypoventilation which is so critical, caused by weakened or paralysed respiratory muscles, as a result, it causes decline in tidal volume, and reduction in alveolar ventilation, which might lead to chronic hypercapnia(10). As low ability of effective cough will gather the mucus and secretions in the airways leading to more exposure for respiratory infections such as pneumonia, bronchitis in CSci population. These infections will exacerbate in long term immobility aligned with cervical spinal cord people, after that, other issues with these population will arise, as some cases will have reduction in ventilation, later, more complications will appear such as limiting of the lungs' capacity and decreasing in their normal functions, as a result, it will lead to hospitalisation frequently(3).

Impairment of the autonomy of breathing due to the autonomic dysfunction impacting the communication between the brainstem and sympathetic nervous system post-injury, contributing to irregular respiratory rhythms and decline in ventilatory drive who lead to both central sleep apnoea and obstructive apnoea because of upper airways muscles weakness. These impairments will lead to nocturnal desaturation and disturbances in deep sleep, because of decrease of oxygenation at night. The previous disturbances will affect the cardiovascular system due to increase in stress level(3). Worsening of the situation and air irritation due to hypoxia will also trigger spikes in the blood pressure which might lead to life-threatening cardiovascular incidents(7). All these disruptions happen in the alignment with autonomic dysreflexia as a spike in blood pressure due to noxious stimuli. Serious issues that might manifest will be arrhythmia, stroke or seizure. This in turn impact the whole homeostatic control mechanism following the injury(7). The weakness of intercostal and accessory muscles will lead to a decline in the lung adequacy and inability to get rid of mucous properly, as the extended parasympathetic activity will trigger consequent problems such as bronchial hyper-secretion, plugging of mucous and atelectasis, as well as, recurrent pneumonia, this exacerbation in respiratory system will often lead to the increase duration for long term ventilatory support(3). After the spinal cord injury takes place, the release of cytokines mainly Tumour necrosis factor-alpha (TNF-a) and Interleukin-6 (IL6) as an inflammatory response will lead to neural apoptosis and synaptic degradation and disrupt synaptic integrity and lead to more tissue damages(16). Post-injury, an excessive surge release of glutamate as central excitatory neurotransmitters leads to excitotoxicity and overstimulate neurones [Fig 6] which affect the phrenic nerve and spinal interneuron negatively in the cervical region, in its turn, lead to reduction of diaphragmatic function and respiratory incoordination(2). Additionally, oxidative stress and mitochondrial dysfunction amplify tissue destruction and diminish the capacity for neuroplasticity(3)The previous issues with phrenic nerve and phrenic interneurons will result in deterioration in the diaphragm functions, hypoventilation, atelectasis and might ends up in a ventilatory failure(1). Chronic respiratory impairment will lead to Progressive lungs disfunction deterioration of quality of life and decline in the physical activities. The inability to clear the mucous properly will lead to more often pneumonia and other respiratory infections(10). Later in life it will cause hypoxia and other cardiovascular issues will develop and get more prominent due to the fact of development of sleep disorder breathing such as central and obstructive apnoea which increase the risk of arrhythmias and hypertension as well(7).

12. Common respiratory complication in Cervical Spinal Cord Injury

12.1 Pulmonary Infections in Cervical Spinal Cord Injury (CSci)

Pulmonary infection such as pneumonia is the most potential cause for death among individuals with cervical spinal cord injury, the issue significantly increases due to inability to cough normally because of weakness of respiratory muscles and disability to clear the lungs mucous as a result or diminish of the mucociliary clearance mechanism, additionally, the increase in the bacterial colonisation significantly rises the risk of developing atelectasis as weakness of diaphragm and accessory muscles comprises lung ventilation creating the best atmosphere for pulmonary infections(10). While complete motor lesion at higher cervical levels has more tendency to develop pneumonia, as the postoperative pulmonary infections in acute CSci patients may be up to 25 percent and are associated with high neurological level, steroid use and the history of smoking according to American spinal injury association (ASIA) grade might lead to respiratory failure in worst case scenario and the need for ventilation or tracheostomy(4).

12.2 Pathophysiology of Pulmonary Infections in CSci

Autonomic dysfunction following cervical spinal cord injury (CSci) will weaken pulmonary immune defences, diminishing pathogen clearance, and secretion retention adds to the risk by creating an infection-prone setting. When damage to the cervical spinal cord takes place, particularly between C3 and C5, it will affect the phrenic nerve function which is critical for diaphragm movement and can cause diaphragmatic dysfunction, reduced ventilation, and poor cough reflex, this retained secretions together with other factors will compromise airway cleaning and elevate the chance of infections such as pneumonia. Following the initial trauma, secondary cascades of responses such as neuroinflammation, oxidative damage and apoptosis lead to further tissue damages. While Glial cells respond by forming a CSPG-dense scar, the activation of reactive glial cells and the creation of chondroitin sulphate proteoglycan (CSPG)-rich glial scar along with the cavities within the spinal cord will disrupt neural communication and plasticity contribution, as well as they impact neuroimmune signalling to cause further decline in respiratory motor function(3).

12.3 Atelectasis and Atypical Presentation of Infections

As pulmonary infections are the main cause of death of individuals with cervical spinal cord injuries (CSci), due their inability to clear their airways secretions properly, the deterioration of their breathing functions, and their disfunction of the nervous system. Atelectasis and pneumonia [Table 2] were among the clearest observations in this population. Atelectasis happens because of the weakness of the diaphragm which is the main inspiratory muscle (C3–C5), intercostal muscles (T1–T11), and accessory breathing muscles. This drastic complication will lead to improper alveolar ventilation and reduction in tidal volume. This disruption might end up in alveolar collapse due to the retention of secretions in the airway. These imbalance affects ventilation-perfusion balance, decrease oxygenation, and make the lungs more exposed to lungs infections. Additionally, the inability to cough normally support the plugging of accumulations in airways and create a proper environment for more frequent pulmonary infections. As pneumonia can particularly be more silent in patients with high-level injuries of the cervical spine region, so it might disrupt autonomic and sensory pathways. Classic symptoms such as chest pain and a productive cough may be absent, requiring healthcare providers to recognize more subtle indicators such as low-grade fever, increased muscle tone, fatigue, changes in secretions, and decreased oxygen levels. These cascades of imbalances will affect ventilation-perfusion matching and make the lungs vulnerable to frequent infections. If left unmanaged, these issues and complications might furthermore develop into acute or chronic respiratory failure, which stay as the main cause of death in these individuals.

Table 2. Common Respiratory Complications in Cervical Spinal Cord Injury. Adapted from Galeiras Vázquez et al. [1].(12)

Complication	Mechanism	Severity	Associated SCI level
Pneumonia	Weak cough, secretion retention	High	C1-C5
Atelectasis	Diaphragmatic dysfunction and mucous plugging	Moderate to high	C1-C5
Sleep apnoea	Impaired ventilatory control and upper airways weakness	moderate	C1-C4
Hypoventilation	Reduce tidal volume and weak inspiratory muscles	High	C1-C6
Mucus plugging	Poor mucociliary clearance and weak abdominal muscles	High	C1-C6

13. Diagnostic Methods for Pulmonary complications Cervical Spinal Cord Injury

Diagnosing pulmonary infection in individuals with cervical spinal cord injury requires combining clinical lab tests, imaging and pulmonary function assessments. Making imaging modalities such as X-ray or CT scan identify characteristic signs of infection, such as consolidation, atelectasis, or pleural effusion(8). When respiratory infection is suspected, Sputum assessments or bronchoalveolar lavage (BAL) are advised whenever sputum samples can be acquired for targeting specific antibiotic treatment. Lab tests such as CBC and C-reactive protein (CRP) detect systemic inflammatory responses, while procalcitonin aids in differentiating bacterial from viral aetiologies (8).

For evaluating respiratory issues in CSci patients, spirometry combined with respiratory muscle strength evaluation should be done, Parameters such as Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), PEF, and Maximal voluntary ventilation (MVV), along with Maximal inspiratory pressure (MIP) and Maximal expiratory pressure (MEP), are evaluated to determine the presence of respiratory insufficiency, these indicators and markers help uncover issues such as insufficient ventilation and ineffective coughing, which are major contributors to pulmonary infections in SCI population(4). Other possible techniques would use multi-electrode arrays which facilitates real-time tracking of spinal interneuron activity in the cervical region, this approach detects synaptic connectivity changes following high cervical injury, altered excitatory or inhibitory pathways may disrupt respiratory control, such changes may compromise respiratory control(3). Another investigational method is Hypoxic Respiratory Stimulation, where the exposure to mild hypoxia can act as a stress test functions as a diagnostic challenge to probe the flexibility and reactivity of respiratory networks in spinal cord injury. A reduced or atypical reaction to hypoxia in chronic SCI cases may point to diminished adaptability and increased vulnerability to pulmonary infections. While a weakened or counterintuitive hypoxic response may suggest limited plasticity and a higher susceptibility to respiratory illness during periods of stress(3). This diagnostic approach may also aid in identifying individuals with residual neuroplasticity as opposed to those with more severe dysfunction(11). Finally, neuroanatomical tracing methods such as WGA-Alexa injections, are still in the experimental phase and not routinely used in clinics to identify respiratory and intraneuronal pathways altered by SCI. These technologies might eventually help tailor diagnostics by revealing damaged or compensatory neural connections and could eventually support personalised evaluations by identifying patients with residual plasticity versus individuals with complete loss of connectivity(8).

14. Management Strategies for Pulmonary complications after Cervical Spinal Cord Injury (CSci)

Approaches to managing pulmonary infections in individuals with cervical spinal cord injury (CSci) include various strategies that focus on rehabilitation and managing the respiratory functions compromised by the injury. Key management objectives include enhancing breathing functions, preventing respiratory complications, and directly manage infections with medical and rehabilitative interventions.

Mechanical Ventilation is necessary for patient at the C5 level injury and above as those types of procedures are crucial for the continuation of their management and treatment process. Since the damage to this level will cause paralysis to diaphragm or drastic weakness, mechanical ventilation in this case will provide a solid solution until the recovery or the adaptation of the breathing capability takes place over time(10).

14.1 Tracheostomy

For patients with cervical spinal cord injury (CSci) who need extended mechanical ventilation, often suggested to undergo an early tracheostomy, it facilitates weaning from mechanical ventilation by reducing airway resistance and dead space, making it easier to wean patients from mechanical ventilation, as well as it provides better airway hygiene through simpler secretion removal which increases comfort and communication for the patient(7).

14.2 Non-Invasive Ventilatory Support (NIV)

Non-invasive ventilation mechanism (NIV) plays a significant role in assisting the populations with cervical spinal cord injuries. The issue in the high level of spinal cord will regularly cause deference in the tidal volume and disability to breath normally, specifically during the sleep, and in turn, the need to utilise the bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) devices. Those mechanisms would help decreasing the need of self-breathing and help in improving the oxygenation without even the need for any invasive procedure such as intubation particularly in cases of chronic hypoventilation and sleep-disordered breathing associated with high cervical level injuries(17). (NIV) has become increasingly popular over the last few decades, and it is notably beneficial in addressing acute and chronic respiratory failures. Positive-Pressure Ventilation is now the leading technique and is provided via various masks or helmets. This technique helps reduce respiratory rates, boost tidal volume, and enhance overall oxygenation and comfort. In contrast, Negative-Pressure Ventilation, which was once prevalent, has largely been replaced by positive-pressure systems. Nevertheless, it is still used for cases, mainly in chronic respiratory failure scenarios(17). NIV proves particularly useful in handling exacerbations of Chronic Obstructive Pulmonary Disease (COPD) and treating cardiogenic pulmonary oedema helping to improve gas exchange and lessen the breathing effort. Post-extubating, NIV can also assist patients particularly when reintubation is considered risky or undesirable(17).

14.3 Mechanical ventilation weaning in acute Tetraplegia

It was realised, that people with high cervical spinal cord injuries, specifically in C1-C4 that mechanical ventilation is necessary due to the completely paralysis of diaphragm, this in turn will help these population with more effective secretion management by providing more stable airways through the tracheostomy procedure for those who need prolonged support. Meanwhile the longer period of mechanical ventilation setup the worst outcomes will appear as it increases the risk of ventilator-associated pneumonia, the damage to trachea, and patients will be more dependent on such strategies, so, in order to decreases the risk of mechanical ventilation and its consequences, it was advised to gradually decrease the ventilator utilisation and start with the ventilator weaning protocols as soon as possible while observing the respiratory muscles functions and oxygenation, as well as, the carbon dioxide level, this mean involving other procedures such as assisted coughing, respiratory physiotherapy and manual chest expansion, additionally, breathing exercises have their massive benefits(6,18).

14.4 Respiratory Muscle Training

This involves methods to enhance the strength of the diaphragm and other supportive muscles, these devices such as respiratory muscle trainers or incentive spirometry can boost inspiratory muscle strength and endurance which can help in easing the weaning from mechanical ventilation, improve cough effect, prevention of atelectasis, and in some scenarios even the reduction of pulmonary infections(19,20). According to one study conducted at a rehabilitation centre in Switzerland examines the relative effects of training intensity and volume on respiratory muscle strength in spinal cord injury patients. The research included Individuals with spinal lesions from C4 to T12. the study concludes that higher intensity training significantly improves muscle strength more than increasing the amount of training. The study revealed that training intensity had a greater effect on respiratory muscle strength than training volume. Specifically, every 10-unit increase in training intensity led to an approximate 7% improvement in PImax and PEmax for individuals with motor complete lesions. This suggests that focusing on the intensity of exercises might be more advantageous for individuals with such injuries, emphasising the importance of personalised respiratory muscle training to enhance lung function and lead in turn to less complication potential in the long run for this population(19). The study further emphasized that the impact of volume alone even with up to 1000 training repetitions resulted in only a 1% gain in strength.

14.5 Secretion Management

As the clearance of secretions is a struggle in CSci individuals due to the impairment of cough reflexes, so the use of cough assist devices is important for the stimulation of coughing and extraction of secretions. In some cases, drainage and chest physiotherapy help in eliminating those secretions from the lungs. Clinical recommendations also support the use of sputum atomization, ambroxol therapy, and mechanical vibration, which have been shown to reduce mucus viscosity, promote gas exchange, and lower the risk of lung infection. Guided cough training, paired with respiratory devices, can significantly enhance airway hygiene and improve oxygenation, especially when integrated with other beneficial ventilatory support strategies(4).

14.6 Phrenic Nerve Stimulation PNS

In certain cases, an option is the electrical stimulation of the phrenic nerve (PNS). It involves implanting a device that applies electrical impulses to the phrenic nerve, inducing diaphragm contractions and simulate natural breathing rhythms. This procedure involves patients with cervical spinal cord injury who retain their phrenic nerve function but at the same time they lost their ability for voluntary respiratory control(10). This kind of stimulation such as diaphragm pacing and (PNS) offers a promising outcome instead of long-term mechanical ventilation. These techniques use the electrical impulses to enhance the diaphragm function directly or through the stimulation of the phrenic nerves which lead to more normal breathing function in the long run, as well as, improving the lungs hygiene. Diaphragm pacing was performed through the laparoscopic by placing the electrodes on the diaphragm or transcutaneous placement through the stimulation of phrenic nerve. These procedures have shown significant improvement reducing the need of mechanical ventilation dependency. These procedures will enhance speech, stimulate olfactory function and overall, the quality of life and social engagements(10).

Recent studies highlighted the possibility of acute intermittent hypoxia (AIH) in enhancing motor function following spinal cord injury particularly when Paired with Task-Specific Respiratory Exercises. Although (AIH) alone offers moderate benefits, its combination with task-specific respiratory training, such as exercises to enhance respiratory strength was vital. This combination has given significantly better outcomes in motor rehabilitation, particularly for limb function, currently being studied for its potential in respiratory recovery. The concept is that (AIH) primes the body’s systems, and focused training further strengthens these pathways. This will potentially lead to better cough mechanics, breath coordination, and airway management which decrease the risks for complications in cervical spinal cord injury patients(9). Recent advances have shown potential strategy for respiratory function preservation, as they introduce astrocyte transplantation through enhanced GLT1 Expression in Transplantation of astrocytes derived from human induced pluripotent stem cells, leading to the preservation of phrenic motor neurones, a reduction in lesion size, and maintain diaphragm innervation. The preservation of these functions is translated into enhanced diaphragm activity as measured by electromyography (EMG) and Compound muscle action potential (CMAP) tests. This technique has shown improvement in the quality of neuroplasticity stimulation in spared spinal pathways, as well as support the motor neurones which play a huge role in breathing(16). Another promising strategy regarding Neuroplasticity and recovery has been manifested in the stimulation of phrenic nerve plasticity and neurotransmitter activity which has been shown in ampakines-based stimulation which stimulate AMPA receptor activity and support synaptic plasticity(5). These compounds promote brain-derived neurotrophic factor (BDNF) expression which help the spinal cord retains intrinsic mechanisms that may allow for partial recovery of phrenic motor function. It will help in reorganization of local interneuron networks that support breathing(2). The changes are mediated by preserved neural pathways, local circuit remodelling, and activity-dependent plasticity within the spinal cord(3).

14.7 Vagus nerve stimulation (VNS)

The enhancement of Respiratory function was manifested also by the stimulation of vagus nerve (VNS) as well, which improves the recovery process as a neuromodulatory therapy that promote motor and autonomic recovery after the injury (9). On the other hand, in animals, (VNS) has helped in the relief of neuroinflammation, facilitate synaptic connectivity, and amplify plasticity in the descending motor circuit, who play a role in respiratory control(1).

The research "Vagus Nerve Stimulation Paired with Rehabilitative Training Enhances Motor Recovery after Bilateral Spinal Cord Injury to Cervical Forelimb Motor Pools" address how the stimuli of vagus nerve play a drastic role post injury of cervical spinal cord patients particularly in forelimb function. This procedure is known for enhancing brain plasticity and neural communication. To test it, they worked with 58 female rats that were trained to perform a task using their front limbs. After injuring the spinal cord in areas important for arm movement (C7/C8), the rats were split into two groups [Fig 5]. one underwent rehab alone, and the other received VNS during their rehab sessions. The stimulation occurred during specific actions involving their forelimbs over six weeks. The VNS-treated group exhibited significantly improved forelimb strength, greater grip performance, and increased spontaneous use of their limbs. These effects extended to untrained behaviours, indicating generalized improvements in motor function. Importantly, the results were not attributable to lesion size reduction or motivational differences, but to enhanced neuroplasticity driven by (VNS)(21).

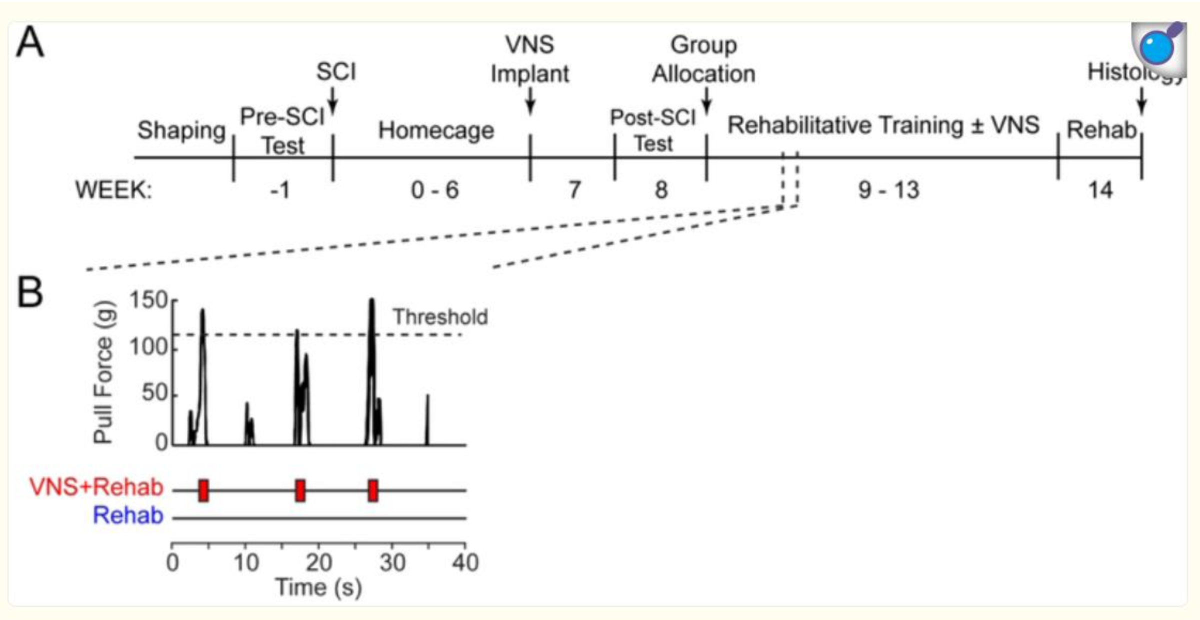

Fig 5. Timeline and protocol for VNS-enhanced rehabilitation after cervical SCI in rats.
(A) Study phases include injury induction, VNS implantation, post-SCI testing, and 5-week training with or without VNS.
(B) Representative pull force data showing VNS (red bars) paired with successful task performance in the VNS+Rehab group.Adapted from: Ganzer PD, Darrow MJ, Meyers EC, et al. Vagus nerve stimulation paired with rehabilitative training enhances motor recovery

after bilateral spinal cord injury to cervical forelimb motor pools. Neurorehabil Neural Repair. 2018;32(7):612–622(21)

15. Rehabilitation strategies for respiratory function improvement in cervical spinal cord injury CSci

15.1 Functional Electrical Stimulation (FES) in Respiratory Rehabilitation

Functional electrical stimulation is an approach where it applies controlled electrical currents to support the weakened or Paralyzed muscles in cervical spinal cord injury population. This procedure is helpful in the enhancement of abdominal and intercostal muscles. It will improve peak expiratory flow (PEF) and has shown gain in expiratory muscles functions, furthermore, was beneficial in coughing improvement(10). This will help patients who have dysfunction with voluntary expiration, as it helps in reduction of mucus, as well as prevent pneumonia and atelectasis. In the long run, it will help to reduce the period of ventilation which improve pulmonary hygiene, and lead to less frequent hospitalisations(10). Pairing (FES) with other strategies such as intermittent hypoxia, or inspiratory muscle training would help the recovery of respiratory function and neural plasticity(6,10). On the other hand, Park et al. acknowledged (FES) as a conventional but limited strategy due to its need for high technical precision and low patient motivation compared to other interactive game based systems(22).

15.2 Respiratory exercise interventions to improve function in tetraplegia

Respiratory disruption is the massive cause of death in population of tetraplegia. Breathing exercises and the incorporation of the physiotherapeutic care in the regular basis have shown a clear improvement in CSci individuals such as air stacking to increase lings volume above the tidal volume level, glossopharyngeal breathing exercises which uses coordinated (gulping) actions to enhance inspiratory pressure and incentive spirometry who contribute massively to enhance the lungs volume and clear the airways, additionally strengthen the inspiratory muscles. In some cases where a massive ineffective cough happens, then a manual abdominal thrust techniques were included to help in expectoration. In a cohort study with 104 SCI patients, 65 of them were tetraplegia patients conducted physiotherapeutic interventions five days a week for 4-8 weeks, was found that these individuals who have been integrated into this rehabilitation approach, where they have been exposed to respiratory muscle training (RMT) were among the most patients who have acquired the best pulmonary function improvement. Forced vital capacity (FVC) increased by 11.7 % in supine position and 12.7 % in sitting position while cough flow enhanced by 22.7 % specially in subacute and chronic phases of tetraplegia individuals.(23). To get rid of the traditional way of the respiratory exercises, another game-based approach was discovered as a respiratory rehabilitation device for better interaction and engagement with this population. This device involved fun multiplayer game formats such as (breathing billiards, breathing tug-of-war, and blowgun darts) [Table 3]. These game-based respiratory rehabilitation devices aimed for inspiratory and expiratory muscles improvement. Patients have shown a definite development in maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), peak expiratory flow (PEF) as well as vital capacity (VC), furthermore, improve the engagement capacity and psychological state in these population by the utilization of this game-based devices(22).

Table 3 Some of the game-based respiratory rehabilitation devices used to increase motivation in tetraplegia patients (22)

Exercise name	**How to perform**	**Targeted function**
Breath Goa-In	Blow a mini ball to score a goal avoiding obstacles	Inspiratory/expiratory volume, strength, peak flow
Lift ball competition	Breath into a cylinder to lift a ball	Inspiratory/expiratory volume and strength
Ball reciprocating count battle	Count how many times a sound senser is triggered by a ball in 7 seconds	Inspiratory/expiratory volume and strength
Breathing tug-of-war	Blow to move a ball toward one’s side in a 2-player tug-of-war	Inspiratory/expiratory volume, strength, peak flow
Breathing curling	Blow a stone toward a curling target board	Inspiratory/expiratory volume, strength, peak flow

Another non-invasive spinal cord stimulation approach involving physical training technique was performed on the cervical spine, using transcutaneous electrical spinal cord neuromodulation (TESCoN) for 2 weeks. This intervention has shown significant difference in inspiratory volume and enhanced coughing function specifically in chronic phases of complete tetraplegia. These clearly points out the importance of these intervention to activate the neural network and plasticity without the need for the invasive procedures or mechanical ventilation. This patient reported enhancement in breathing function and coughing from supine position for first time post-injury(24)

Table 4 Summary of respiratory exercises (22–24)

Intervention type	**Duration**	**Participants**	**Improvements**
Self-directed respiratory muscle training RMT	4-8 weeks	104 SCI patients, 65 tetraplegics	FVC 11.7 %-12.7 % PCF 22.7 %
Game-based respiratory exercise devices	8 weeks, 60 min/session	2 patients with C6 tetraplegia	MIP 66-84 VC 0.84-0.89 L PEF 2.3 L/s
Transcutaneous electrical spinal cord neuromodulation (TESCon)	2 weeks, 60 min/day	1 patient with chronic C5 tetraplegia	Increased FEV 1, inspiratory volume and cough strength

15.3 Routine Supportive Care Measures

Basic routine supportive respiratory will be as important as another advance neurorehabilitation strategies as it is the basic level of interventions in patients with cervical spinal cord injuries. As assistive care in clearing mucous enhances the coughing mechanism. Chest physiotherapies are as important in prevention of secretion accumulation which reduce the risk of complications such as pneumonia and atelectasis. On the other hand, the ability to handle sleep-disordered breathing (SDB) particularly obstructive or central sleep apnoea require non-invasive ventilation during sleep which reduce the complications, improve oxygenation and support the respiratory functions in tetraplegia individuals(20).

Respiratory treatment in populations with cervical spinal cord injury patients must be highly considered as a dynamic and continuous procedures. While the earlier interventions such as mechanical ones performed in these patients, the earlier move towards other training approaches and other assistive technologies and helping these individuals out maintaining their respiratory functions later in life. Specialised educational protocol will eventually support these individuals maintaining their respiratory health, so, caregivers play a huge role in this aspect explaining any early signs of respiratory distress, and other consequences follow ups, such as assisted coughing, preventions of future complication and pulmonary infections which lead to the best outcomes and early transition to home care(20).

Table 5. Summary of respiratory phases after cervical spinal cord injury, Park J, Kang D, Eun SD. Development and pilot testing of novel game-based respiratory rehabilitation exercise devices for patients with tetraplegia. Technology and Health Care. 2021;29(6):1119–27. Shin JC, Han EY, Cho KH, Im SH. Improvement in Pulmonary Function with Short-term Rehabilitation Treatment in Spinal Cord Injury Patients. Sci Rep. 2019 Dec 1;9(1). Gad P, Kreydin E, Zhong H, Reggie Edgerton V. Enabling respiratory control after severe chronic tetraplegia: an exploratory case study. J Neurophysiol (22–24).

Phase	**Time since injury**	**Key features**	**Main rehabilitation intervention**
Acute	0-14 days	Severe respiratory muscle paralysis, and high risk of complication such as pneumonia	Incentive spirometry glossopharyngeal breathing Air stacking Abdominal thrust
Subacute	2-8 weeks	Partial neurological recovery and moderate respiratory disruption	Self-directed inspiratory muscle training Air stacking Glossopharyngeal breathing Incentive spirometry

Chronic	Greater than 8 weeks	Stabilized with reduced function and persistent ventilatory deficits	Game-based respiratory exercises Transcutaneous electrical spinal cord neuromodulation (TESCon)

16. Preventive Strategies for Pulmonary Infections in cervical spinal cord injury (CSci)

Monitoring and observation of individuals with tetraplegia is a vital technique in both acute and chronic phase of cervical spinal cord injury by using the instruments such as pulse oximetry SpO2, capnography and spirometry would play a drastic role in finding out any early marks of any decrease in ventilation or accumulation of the secretions in the airways. Additionally early detection of any signs of autonomic dysreflexia should be highly considered as it might worsen the outcomes of respiratory function status, these early detections will help in prevention in such severe complications in these people such as pneumonia or respiratory failure and allow for early interventions(6).

Effective prevention of pulmonary infections in patients with cervical spinal cord injury (CSci), such as muscle debility, retention of secretions, and impaired ventilation control, is vital, on the other hand, an effective strategy for prevention is the use of intermittent hypoxia therapy, this method repeatedly subjects the patient to mild hypoxia, inducing adaptive changes in the respiratory motor system aiding in the reestablishment of normal breathing patterns and decreasing the likelihood of infections(2). One of the earliest interventions that could reduce the secondary damage is administering methylprednisolone soon after an injury which can diminish inflammation, and minimising damage by limiting immune-mediated neuronal impairment to the spinal cord potentially maintaining respiratory function(10). Another critical procedure is surgical decompression which may alleviate spinal cord pressure potentially. It will improve the impact of the injury specifically within the first 24 hours post-injury, and leading to better outcomes, including improved respiratory functions due to the reduction of ischemia and tissue loss(6). Additionally, Preclinical research indicates that substances such as ginsenosides may enhance neurological function and provide antioxidant effect, this will track the development of treatments targeting the reduction of oxidative stress and secondary damage following an injury. It will potentially aid in the preservation of respiratory function post Sci(10). In terms of regenerative interventions, the transplantation of neuronal progenitor cells or other stem cells offer promising new techniques to restore or augment respiratory pathways following Sci. Therapies that enhance the survival and integration of these cells might effectively restore connections in the phrenic circuitry, essential for respiratory functionality by restoring diaphragm activity. Finally, it is crucial to closely monitor SCI patients for respiratory distress and other complications, such as autonomic dysreflexia and should be a key aspect for their ongoing care plan to ensure early intervention and individualised respiratory support(10).

17. Summary of Therapeutic Interventions

Integrations of a comprehensive approaches in population with cervical spinal cord injuries have become of priority as a best therapeutic intervention managing the respiratory dysfunctions in these populations such as combining neuroplasticity-based techniques and supportive care. All procedures from mechanical ventilation and non-invasive support to other advance methods such as diaphragm pacing, functional electrical stimulation, and intermittent hypoxia contribute to efficiently maintaining respiratory capabilities, while individuals' rehabilitation plans, and regular observations play a role improving the quality of life and long-term respiratory health maintenance(6,10,25).

17. Overview of Findings and Discussion

Respiratory impairment following cervical spinal cord injury in tetraplegia patients is one of the most complicating issues in these population and remain as a huge challenge in neurorehabilitation point of view. As respiratory problems stay the leading cause of morbidity and mortality in tetraplegic patients. This thesis has gone through all aspects of respiratory disfunctions in CSci from impairment in the neural pathway and declined muscle activation to disruption of mucous clearance(2,6,10). It has highlighted potential pulmonary infections risks such as pneumonia and atelectasis post injuries and all possible interventions utilised to manage them. Various therapeutic interventions were examined depending on the injury level, respiratory reserve, and rehabilitation stage, including Mechanical ventilation and tracheostomy who are essential in the acute phase for patients with high cervical lesions(7). While non-invasive ventilation (NIV) was vital, particularly during sleep to manage nocturnal hypoventilation(17). While some advances confirmed that respiratory muscle training has proven to increase inspiratory and expiratory muscle strength, especially when performed at high intensity(19) Other advances suggest that functional electrical stimulation (FES) is useful for strengthening abdominal and intercostal muscles, as well as enhancing airway clearance(10), and intermittent hypoxia (AIH) was used to promotes neuroplasticity in respiratory motor pathways and improves both limb and breathing function(9) While Diaphragm pacing has an effective alternative to long-term ventilation in patients with intact phrenic nerves(10), Vagus nerve stimulation (VNS) showing neuromodulatory benefits by enhancing respiratory plasticity and autonomic balance(1). Additionally, more novel experimental approaches such as stem cell transplantation and astrocyte therapy show potential in preserving phrenic motor neurons and restoring respiratory circuits(16) These findings support a multimodal respiratory rehabilitation approach, with the goal of reducing dependency, preventing complications, and ultimately improving respiratory independence and quality of life in individuals with CSci.

Most studies agree that impairment to the descending pathways -particularly those innervating the diaphragm through the phrenic nerve will result in decline in lung capacity, inability to cough properly, as well as high risk later for pulmonary infections(6). Meanwhile not all advances pointed out the efficacy of the integration of the interventions such as IMT, AIH, FES, VNS as it might differs in the sense of complete vs incomplete injuries and their incorporation and application in the real-life rehab-protocols(9).

AIH showed improvement in motor output and stimulating neuroplasticity by application of serotonergic pathways and BDNF expression(3), meanwhile other studies warned about the potential of more inflammatory risks of prolonged or high dose exposure particularly in chronic cases(16). While FES was found to be very beneficial in having better ventilation and adequate coughing in incomplete CSci, it still doesn’t provide same benefit when it comes to the lowest motor neurone (LMN) damage, as long-time use could possibly lead to muscle fatigue and skin irritation(10). Additionally, VNS as the most clinically tested among other procedures, some studies suggested that its anti-inflammatory and plasticity-inducing effect still lacks strong human data and outcomes specifically in its effect on autonomic stability in injuries in the high cervical level of spinal cord(2). Game-based rehabilitation programs have been introduced as a beneficial way to increase interaction with the and improve the motivation by stimulating the mentality behaviour in this population. While more advanced approaches such as transcutaneous electrical spinal cord neuromodulation (TESCon) have been used to enhance respiratory-related neuroplasticity and activate the spinal pathway.(22)

and management of the secretions. It was recommended to perform spirometry regularly, induce patents educational level, as well as multidisciplinary follow-up for less complication's potential. The combination of efficient prevention approaches with proactive rehabilitation will provide the best respiratory recovery outcomes after tetraplegia.

19.Neuroplasticity and the Future of Respiratory Rehabilitation

Many studies have addressed the importance of neuroplasticity-based interventions as it has shown a shift in the management of respiratory dysfunctions in CSci individuals such as acute intermittent hypoxia (AIH) and functional electrical stimulation (FES), these strategies reactivate the neural pathways and improve the communication within the spinal cord(2,10). These studies have shown greater early independence of mechanical ventilator, as well as a clear enhancement in respiratory drive and strengthen the related respiratory muscles(9,25).

20. Traditional vs. Advanced Respiratory Therapies

Many studies have confirmed that traditional procedures such as mechanical ventilation, non-invasive ventilatory support and cough assisting have been the foundation of respiratory care in population of spinal cord injuries. These procedures have been important interventions in prevention of the complications in these individuals such as pneumonia and atelectasis by improving airway clearance(10,26). These techniques help in providing crucial support, while other advanced strategies including phrenic nerve enhancement, and diaphragm pacing, as well as neuroplasticity-driven management such as AIH and FES, these modalities promote muscle reconditioning, stimulate plasticity within spared circuits, and enhance respiratory independence functions of respiratory system(6,10,25).

21. Clinical challenges and limitations

Although all the previous advances in respiratory management, still many issues appear in optimising support for individuals with cervical spinal cord injuries due to the complexity and variability in the injury severity. It makes it a bit challenging to administer treatment protocols among all these patents(2). Possibilities of the advance interventions such as phrenic nerve enhancement, diaphragm pacing was limited to specialised Centres, where it might limit the availability for many individuals. Even other interventions such as intermittent hypoxia therapy as the long-term need for rehabilitation make the situation even more challenging specifically for sleep apnoea management and muscle training(20).

22. Future Directions and Clinical Recommendations

It is suggested by many advances in this section to standardise protocols for individuals and prioritize large-scale clinical trials to validate neuroplasticity-enhancing interventions such as AIH and FES(2,10). In the respiratory level, engaging early assessment and personalised therapy plans, as well as rehabilitation programs possibly improve the outcomes, furthermore, the wide spread of training multidisciplinary team for emerging technologies will definitely enhance the results(19,25)

23. Conclusion:

One of the most life-threatening complications of tetraplegia were the accompanied disruption of respiratory functions in these populations. The impairment begins from the descending neural pathways reaching the respiratory muscles involving the diaphragm, intercostal muscles, and accessory muscles, it leads to hypoventilation, inability to cough normally and the increase potential for the pulmonary infections such as pneumonia and chronic respiratory dysfunction later in life. It needs deep understanding of the underlying pathophysiology and adapted individual plans for each patient in the neurological level, as well as to assess the injury and its severity, additionally, consequent functionalities potential post injuries(18,20).

Involving both supportive approaches and neurorehabilitation methods in the management of respiratory dysfunctions in CSci have been administered and emphasized in recent studies, it was highly emphasized to maintain airway clearance and prevent complications by utilising variant approaches such as mechanical ventilation, non-invasive ventilatory support, as well as assisted coughing. Additionally, the recent use of intermittent hypoxia therapy, functional electrical stimulation (FES), diaphragm pacing, phrenic nerve enhancement which aimed to restore function by neuroplasticity shifting to the best rehabilitation intervention which aim for early respiratory independence and improve the quality of life in the long run for these individuals(5,10,25).

Still ongoing advances to widely develop more possibilities for people with tetraplegia to support them by offering potential opportunities for autonomy through combining both traditional and more targeted plasticity strategies specifically when addressed earlier post-injury, which support respiratory motor output and independence, as well as reduce complications. The concept of activity-dependent plasticity supports these techniques for recovering of respiratory functions and get rid of most possible complications. It is advised to include everyday clinical practices through these advancements(16). Moving forward, emphasis should be placed on standardizing treatment protocols, launching large-scale clinical trials, and ensuring the availability of multidisciplinary rehabilitation. These efforts will help transform innovative approaches into routine care, restore function, stimulate autonomy and improve outcomes for individuals with tetraplegia(2).

24. References

1. Fallahi MS, Azadnajafabad S, Maroufi SF, Pour-Rashidi A, Khorasanizadeh MH, Sattari SA, et al. Application of Vagus Nerve Stimulation in Spinal Cord Injury Rehabilitation. Vol. 174, World Neurosurgery. Elsevier Inc.; 2023. p. 11–24.
2. Hormigo KM, Zholudeva L V., Spruance VM, Marchenko V, Cote MP, Vinit S, et al. Enhancing neural activity to drive respiratory plasticity following cervical spinal cord injury. Vol. 287, Experimental Neurology. Academic Press Inc.; 2017. p. 276–87.
3. Gonzalez-Rothi EJ, Allen LL, Seven YB, Ciesla MC, Holland AE, Santiago J V., et al. Prolonged intermittent hypoxia differentially regulates phrenic motor neuron serotonin receptor expression in rats following chronic cervical spinal cord injury. Exp Neurol. 2024 Aug 1;378.
4. Luo K, Huang YQ, Zhu LB, Gan XR, Zhang Y, Xiao SN, et al. Risk Factors and Nomogram for Postoperative Pulmonary Infection in Patients with Cervical Spinal Cord Injury. World Neurosurg. 2023 Sep 1;177:e317–24.
5. Sandhu MS, Perez MA, Oudega M, Mitchell GS, Rymer WZ. Efficacy and time course of acute intermittent hypoxia effects in the upper extremities of people with cervical spinal cord injury. Vol. 342, Experimental Neurology. Academic Press Inc.; 2021.

6. Galeiras Vázquez R, Rascado Sedes P, Mourelo Fariña M, Montoto Marqués A, Ferreiro Velasco ME. Respiratory management in the patient with spinal cord injury. Vol. 2013, BioMed Research International. 2013.

7. Jian Y, Zhang Z. The Dose-Response Relationship Between Age and Tracheostomy in Patients with Traumatic Cervical Spinal Cord Injury: A Restricted Cubic Spline Function Analysis. World Neurosurg. 2023 Feb 1;170:e380–6.

8. Yoshida R, Kawamura K, Setaka Y, Woo H, Ishii N, Mizukami M, et al. Rib cage contributions to inspiratory capacity in patients with cervical spinal cord injury. Curr Res Physiol. 2024 Jan 1;7.

9. Arnold BM, Toosi BM, Caine S, Mitchell GS, Muir GD. Prolonged acute intermittent hypoxia improves forelimb reach-to-grasp function in a rat model of chronic cervical spinal cord injury. Vol. 340, Experimental Neurology. Academic Press Inc.; 2021.

10. Ragnarsson KT. Functional electrical stimulation after spinal cord injury: Current use, therapeutic effects and future directions. Vol. 46, Spinal Cord. 2008. p. 255–74.

11. Webster LR, Karan S. The Physiology and Maintenance of Respiration: A Narrative Review. Vol. 9, Pain and Therapy. Adis; 2020. p. 467–86.

12. Galeiras Vázquez R, Sedes PR, Fariña MM, Marqués AM, Elena M, Velasco F. Respiratory Management in the Patient with Spinal Cord Injury. Biomed Res Int [Internet]. 2013 Jan 1 [cited 2025 May 3];2013(1):168757. Available from: /doi/pdf/10.1155/2013/168757

13. Schepici G, Silvestro S, Mazzon E. Regenerative Effects of Exosomes-Derived MSCs: An Overview on Spinal Cord Injury Experimental Studies. Vol. 11, Biomedicines. MDPI; 2023.

14. Introduction - SCIRE Professional [Internet]. [cited 2025 May 3]. Available from: https://scireproject.com/evidence/respiratory-management-rehab-phase/introduction/

15. Neural Control of Ventilation - Involuntary Control - TeachMePhysiology [Internet]. [cited 2025 May 3]. Available from: https://teachmephysiology.com/respiratory-system/regulation/neural-control-ventilation/

16. Seven YB, Allen LL, Ciesla MC, Smith KN, Zwick A, Simon AK, et al. Intermittent Hypoxia Differentially Regulates Adenosine Receptors in Phrenic Motor Neurons with Spinal Cord Injury. Neuroscience. 2022 Dec 1;506:38–50.

17. Noninvasive Ventilation [Internet]. 2020. Available from: https://emedicine.medscape.com/article/304235-overview?form=fpf

18. Ehrlich M, Manns PJ, Poulin C. Respiratory training for a person with C3-C4 tetraplegia.

19. Raab AM, Krebs J, Pfister M, Perret C, Hopman M, Mueller G. Respiratory muscle training in individuals with spinal cord injury: effect of training intensity and -volume on improvements in respiratory muscle strength. Spinal Cord. 2019 Jun 1;57(6):482–9.

20. Berlowitz DJ, Wadsworth B, Ross J. Respiratory problems and management in people with spinal cord injury. Breathe. 2016;12(4):328–40.

21. Darrow MJ, Torres M, Sosa MJ, Danaphongse TT, Haider Z, Rennaker RL, et al. Vagus Nerve Stimulation Paired With Rehabilitative Training Enhances Motor Recovery After Bilateral Spinal Cord Injury to Cervical Forelimb Motor Pools. Neurorehabil Neural Repair. 2020 Mar 1;34(3):200–9.

22. Park J, Kang D, Eun SD. Development and pilot testing of novel game-based respiratory rehabilitation exercise devices for patients with tetraplegia. Technology and Health Care. 2021;29(6):1119–27.

23. Shin JC, Han EY, Cho KH, Im SH. Improvement in Pulmonary Function with Short-term Rehabilitation Treatment in Spinal Cord Injury Patients. Sci Rep. 2019 Dec 1;9(1).

24. Gad P, Kreydin E, Zhong H, Reggie Edgerton V. Enabling respiratory control after severe chronic tetraplegia: an exploratory case study. J Neurophysiol [Internet]. 2020;124:774–80. Available from: https://figshare.com/s/2687f22930e3a0ee21c0

25. Vose AK, Welch JF, Nair J, Dale EA, Fox EJ, Muir GD, et al. Therapeutic acute intermittent hypoxia: A translational roadmap for spinal cord injury and neuromuscular disease. Exp Neurol. 2022 Jan 1;347.

26. Pizzolato C, Gunduz MA, Palipana D, Wu J, Grant G, Hall S, et al. Non-invasive approaches to functional recovery after spinal cord injury: Therapeutic targets and multimodal device interventions. Vol. 339, Experimental Neurology. Academic Press Inc.; 2021.