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Review

Electrostimulation as a method of correction of respiratory disorders in patients with cervical spinal cord injury: A review

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BACKGROUND: Patients with cervical spinal cord injury have the highest risk of developing respiratory dysfunction and associated complications such as pneumonia, atelectasis, and respiratory failure. Respiratory dysfunction is the leading cause of comorbid, somatic, and infectious pathology, and mortality following traumatic cervical spinal cord injuries. Mechanical ventilation of the lungs is the standard treatment for such patients; however, it is associated with atrophy and diaphragm dysfunction.

AIM: To analyze literature data on the use of electrical stimulation techniques of the spinal cord, nerves, and muscles for the correction of respiratory disorders in patients with cervical spinal cord trauma.

MATERIALS AND METHODS: This study presented the results of the search and analysis of peer-reviewed articles that examined the effects of various electrical stimulation techniques on respiratory function in patients with cervical spinal cord injury. ScienceDirect, Google Scholar, and PubMed were searched from 2000 to 2022.

RESULTS: Currently, new treatment options are available for patients with tetraplegia, with reduced ventilatory function. Many studies have shown the positive effect of electrostimulation techniques on ventilatory function such as reduced time spent on mechanical ventilation and reduced incidence of infections and other lung complications.

CONCLUSIONS: Electrical stimulation promotes neuromuscular plasticity and results in improved spontaneous activation of the diaphragm and respiratory muscles. Electrostimulation in a comprehensive rehabilitation program of patients with traumatic spinal cord injuries at the cervical level is currently employed to promote weaning from mechanical ventilation and prevent accompanying complications such as respiratory failure, pneumonia, and atelectasis. In addition to invasive electrical stimulation of the diaphragmatic nerve and/or spinal cord, existing less invasive electrostimulation techniques require further investigation in patients with spinal cord injury and respiratory dysfunction.

Keywords: transcutaneous spinal cord stimulation; spinal cord stimulation; epidural spinal cord stimulation; neuromodulation; neuroprosthesis; electrical stimulation; functional electrical stimulation; muscle stimulation; respiration; cough; inspiratory; expiratory.

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Научный обзор

Электростимуляция как метод коррекции респираторных расстройств у пациентов с травмой шейного отдела спинного мозга (обзор литературы)

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Обоснование. У пациентов с травмой шейного отдела спинного мозга наибольший риск развития дыхательной дисфункции и сопутствующих осложнений, таких как пневмония, ателектаз и дыхательная недостаточность. Дыхательные расстройства — ведущая причина развития сопутствующей соматической, инфекционной патологии и смертности после травматического повреждения шейного отдела спинного мозга. Механическая вентиляция легких является спасительным стандартом лечения таких больных и ассоциирована с атрофией и дисфункцией диафрагмы.

Цель — проанализировать литературные данные, содержащие информацию о методиках электростимуляции спинного мозга, нервов и мышц для коррекции респираторных расстройств у пациентов с травмой шейного отдела спинного мозга.

Материалы и методы. В статье представлены результаты поиска и анализа рецензируемых статей, в которых изучали влияние различных методик электростимуляции на дыхательную функцию у пациентов с травмой шейного отдела спинного мозга. Поиск выполнен на платформах ScienceDirect, Google Scholar, PubMed за период с 2000 по 2022 г.

Результаты. В настоящее время разработаны новые варианты лечения пациентов с тетраплегией, со сниженной вентиляционной функцией легких. Множество исследований показывают положительное воздействие методик электростимуляции на вентиляционную функцию легочной ткани в виде уменьшения сроков нахождения на искусственной вентиляции легких, количества инфекционных и других осложнений со стороны легких.

Заключение. Электростимуляция способствует нервно-мышечной пластичности и улучшению спонтанной активации диафрагмы и дыхательных мышц. Включение электростимуляции в комплексную программу восстановительного лечения больных с травматическими повреждениями спинного мозга на шейном уровне — стратегия, используемая в настоящее время для содействия отмене искусственной вентиляции легких и борьбе с сопутствующими негативными эффектами, такими как дыхательная недостаточность, пневмония, ателектаз. Помимо инвазивной электростимуляции диафрагмального нерва и/или спинного мозга, существуют менее инвазивные методы электростимуляции, которые необходимо изучать для применения у пациентов с нарушением функции дыхании при травме спинного мозга.

Ключевые слова: транскутанная стимуляция спинного мозга; стимуляция спинного мозга; эпидуральная стимуляция спинного мозга; нейромодуляция; нейропротезирование; электростимуляция; функциональная электростимуляция; стимуляция мышц; дыхание; кашель; инспираторный; экспираторный.

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BACKGROUND

According to clinical guidelines for the treatment of acute unstable injury and spinal cord injury, the incidence of spinal fractures ranges from 5.5% to 17.8% among musculoskeletal injuries. Patients with acute complicated spinal injury account for 2%–3% of all patients admitted to neurosurgical departments [1].

Cervical spinal cord injury leads to life-threatening paralysis of the respiratory muscles and reduced breathing capacity. Approximately 40% of all patients with injury in this segment of the spinal cord require mechanical ventilation, and in 5% of patients, chronic artificial lung ventilation (ALV) is needed [2].

Patients with cervical spinal cord injury are at the highest risk of developing respiratory dysfunction and associated complications such as pneumonia, atelectasis, and respiratory failure [3, 4].

Respiratory disorders are the major causes of concomitant somatic and infectious diseases and mortality after traumatic cervical spinal cord injury [5, 6].

With advances in medical care, the average life expectancy of patients with spinal cord injuries has increased over the past 50 years, whereas the number of patients discharged with ALV dependence has increased [7, 8].

Mechanical ventilation of the lungs is a life-saving standard of care for these patients; however, it is associated with diaphragm atrophy and dysfunction, resulting in a restrictive ventilation disorder. A study demonstrated the presence of basic bronchoconstriction in these patients, which is explained by the interrupted sympathetic innervation of the lungs [9]. The inclusion of electrical stimulation in comprehensive rehabilitation therapy of patients with traumatic cervical spinal cord injuries is a strategy currently used to facilitate ALV cessation and combat the associated negative effects. Many studies have shown that electrical stimulation can promote neuromuscular plasticity and improve spontaneous activation of the diaphragm and respiratory muscles [10–15].

These results suggest the need to reassess the role of respiratory rehabilitation in patients with cervical spinal cord injury and consider new models for their rehabilitation and care.

The work aimed to analyze literature data containing information on electrical stimulation of the spinal cord, nerves, and muscles for the treatment of respiratory disorders in patients with cervical spinal cord injury.

MATERIALS AND METHODS

The study presents the results of a search and analysis of peer-reviewed articles that evaluated the effect of various electrical stimulation techniques on respiratory function in patients with cervical spinal cord injury.

The search was performed on ScienceDirect, Google Scholar, and PubMed for articles published between 2000 and 2022. The following keywords were used: *transcutaneous spinal cord stimulation, diaphragm pacing, spinal cord stimulation, epidural spinal cord stimulation, neuromodulation, neuroprothesys, stimulation, electrical stimulation, functional electrical stimulation, muscle stimulation, respiration, cough, spirometry, tidal volume, inspiratory,* and *expiratory*.

Articles that described electrical stimulation and assessed the patient's respiratory function during therapy were included in the analysis. Duplicate articles (or if research participants were not independent of the previous publication) and editorial articles were excluded.

Initially, all abstracts were reviewed and sorted based on the predefined inclusion criteria. The full texts of studies that met these criteria were then reviewed and again selected based on predetermined inclusion criteria. A total of 68 articles were analyzed.

RESULTS AND DISCUSSION

Physiology of respiration before and after spinal cord injury

The temporal and coordination characteristics of respiration are complex and include various neuronal populations that control several muscle groups (Fig. 1). Automatic central control of respiratory rhythm occurs in the respiratory centers of the brainstem after the integration of sensory feedback. Bulbospinal inputs synapse to premotor and motor neurons of the phrenic nerves in the cervical spinal cord (segments C_{III}–C_{V}). The bilateral phrenic nerves innervate the main inspiratory muscle, i.e., the diaphragm, which contracts, thereby expanding the chest cavity and increasing the lung volume for the mechanical exchange of inhaled gases. Rhythmogenic respiratory centers of the brainstem also synapse with motor neurons of the thoracic spinal cord, which ultimately innervate the external intercostal muscles responsible for expanding the chest during inspiration; this is mainly contributed by the T_{I}–T_{III} segments, and the more caudal motor neurons of the thoracic spinal cord complement their work in varying degrees. Accessory respiratory muscles used for active breathing and after injury include the sternocleidomastoid, scalenus, oblique, rectus abdominis, pectoralis, and internal intercostal muscles.

The diaphragm can be contracted by will, and the main regulation is implemented automatically depending on the level of CO_2 monitored by the respiratory brain centers. When the diaphragm relaxes, air is exhaled because of the elastic recoil of the lungs and pleural cavity. During forced expiration, such as when coughing, the internal intercostal muscles and abdominal wall muscles function antagonistically to the diaphragm.

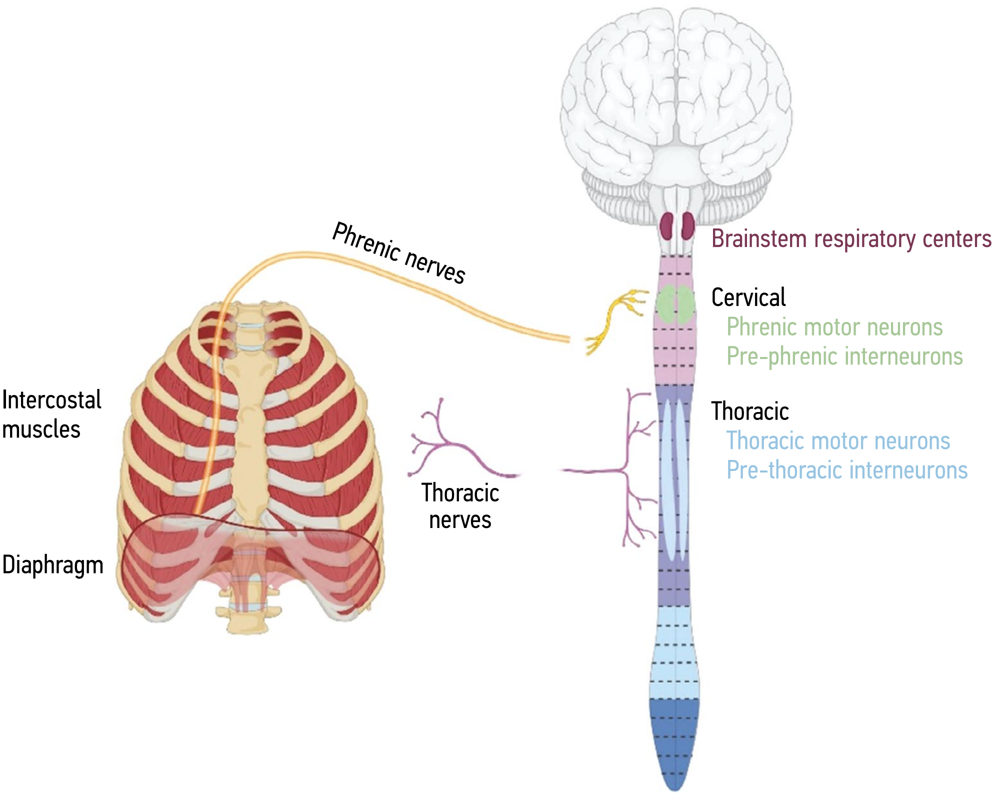

Fig. 1. Central organization of the neural control of breathing

Cervical spinal cord damage leads to paralysis or paresis of the respiratory muscles that is, a decrease in respiratory function and airway patency because of damage to the pathways leading from the ventilation centers in the brainstem to the motor neurons of the respiratory muscles in the cervical (*n. phrenicus*) and chest (e.g., *nn. intercostalis*) parts of the spinal cord [16, 17].

With high-level cervical spine injuries that is, above segment C_{III} of the spinal cord, the spinal roots, which are directly part of the phrenic nerves and innervate the diaphragm, remain intact; however, the axons, passing from the respiratory centers in the medulla oblongata to the spinal cord, are interrupted. Such patients will require exogenous ventilation in the future [18].

Emerging respiratory failure is the most common cause of comorbidities and mortality in both acute and chronic periods of spinal cord injury [3, 19, 20].

In patients with spinal cord injury, even without the need for mechanical lung ventilation during the daytime, breathing can be disturbed during sleep [3, 21] and caused a decrease in the ability to induce a cough to protect the airways, which significantly increases the risk of life-threatening conditions such as atelectasis and pneumonia [3, 22]. In some cases, disconnection from the ventilator is possible [23]; however, tolerance to respiratory loads often remains significantly reduced [24].

In the first weeks after injury, patients with cervical spinal cord damage are at risk of respiratory arrest. Sometimes, it is associated with simultaneous chest trauma. Paralysis of the intercostal muscles leads to a loss of 40% of vital capacity, and the loss of sympathetically mediated bronchial dilatation can further increase the risk of respiratory failure. Inhaled bronchodilators are usually used in the acute phase after spinal cord injury. Despite such treatment, excessive mucus production and secretion stagnation are noted. An imbalance of the autonomic nervous system in this condition can be life-threatening because a patient with a cervical spinal cord injury, prone to hypoxia, may experience severe bradycardia or cardiac arrest during tracheal sanitation. Tracheal irritation is a strong stimulus for the vagal reflex even in healthy individuals; in patients with spinal cord injury, the response increases because of the loss of supraspinal control of the sympathetic nervous system.

Exposure to exogenously imposed ventilation through a respiratory apparatus can adversely and chronically affect the patient. Intrinsic muscles are not stimulated but are passively set in motion. The study compared diaphragm biopsy specimens from 14 brain-dead organ donors who received mechanical ventilation and eight control patients without mechanical ventilation [25]. Organ donors were mechanically ventilated for 18–69 h. After 18 h of positive-pressure ventilation, the diaphragm fibers showed marked atrophy, with 57% and 53% decrease in slow twitch type I fibers and fast twitch fibers, respectively. Active muscle areas atrophied faster, which caused oxidative stress and increased proteolysis [25].

In acute or chronic respiratory failure, positive-pressure mechanical ventilation may be life-sustaining. Some patients tolerate less invasive mechanical ventilation; however, most patients initially receive positive-pressure ventilation through a tracheostome [26].

A comparative analysis of the life expectancy of healthy people and 20-year-old patients with spinal cord injury showed that life expectancy with long-term mechanical ventilation is noticeably reduced from 58.6 to 17.1 years. According to the US National Spinal Cord Injury Database 2002, the survival rate of patients without ventilation was 84%, whereas with ventilation, it was only 33% [27].

In addition, mechanical ventilation creates additional obstacles to the mobility and independence of a patient with impaired motor function of the limbs resulting from an injury and causes varying degrees of physical discomfort and impaired speech and olfaction [28].

Full mechanical ventilation can make it impossible for the patient to stay at home, and in this case, long-term facilities bear much of the responsibility for care. Care for the ventilated patient includes day and night surveillance by trained personnel. The caregiver must manipulate the ventilator settings to optimize respiratory function and adapt to intermittent changes in oxygenation. In addition, adequate drainage of the lungs must be ensured by methods such as chest percussion (to facilitate discharge) or frequent debridement [29].

Correction methods

Installation of a respiratory pacemaker

Respiratory pacemaker implantation involves the patient carrying a device that uses electrical impulses to achieve a specific function.

The device contains an external transmitter and receivers. The receivers are connected to electrodes that are sutured to the phrenic nerves at the anterior surface level of the neck or along the course of the nerve in the chest cavity. Laparoscopic installation is an alternative method. The procedure includes visualization of the abdominal surface of the diaphragm using laparoscopy, electrophysiological mapping of the muscle to determine the main motor point and optimal contraction, and surgical implantation of stimulating electrodes in this site.

Currently, the most common indication for pacemaker installation in spinal cord injury is tetraplegia above level C_{III}, types A and B according to the ASIA classification [30–32]. Patients with tetraplegia must have respiratory paralysis requiring mechanical ventilation, viable phrenic nerves, do not have lung disease, and must be conscious.

Clinical studies revealed that electrical stimulation of the diaphragm not only reduces or eliminates the need for mechanical ventilation [18, 33] but also contributes to the gradual restoration of spontaneous breathing [34, 35]. Diaphragmatic stimulation was suggested to cause neuroplastic changes in the respiratory system and promote its recovery in patients with spinal cord injury [36]; however, the mechanisms involved remain unknown.

The avoidance of exogenous ventilation results in lowered airway pressure, increased posterior lung ventilation, and maintenance of negative chest pressure [29]. Phrenic nerve stimulation is closer to natural respiratory activity because inhalation is induced by the formation of negative pressure due to the contraction of intrinsic muscle fibers in contrast to exogenously induced inflation. Speech quality and olfaction are improved, which in turn promotes overall well-being [28]. Avoiding constant dependence on ALV also appears to make the patient more mobile at home and community and therefore may lead to greater reintegration.

In some patients with ventilation-dependent tetraplegia, phrenic nerve function was preserved only on one side. Thus, these patients were not candidates for respiratory pacemaker installation. In four patients, combined unilateral stimulation of the phrenic nerve and intercostal muscles was evaluated. Combined stimulation resulted in an increase in the maximum inspiratory volume from 600 mL to 1300 mL. Moreover, two out of four patients could achieve complete independence from ALV, whereas the rest felt comfortable without mechanical ventilation for 12–16 h a day.

Despite all the benefits of a diaphragmatic pacemaker, this technique allows achieving complete lung ventilation in patients with ventilator-dependent tetraplegia only in approximately 50% of cases [37–39].

The lack of greater success with this method has several potential explanations. First, this method does not activate the intercostal muscles, which are responsible for approximately 40% of vital capacity [39–42].

Second, chronic stimulation of the phrenic nerves changes the ratio of type I and II muscle fibers over time from a uniform distribution to a greater distribution of type I fibers, which are characterized by high endurance but reduced strength, resulting in a smaller volume of inhaled air. Finally, this electrode technology does not provide full diaphragm activation, which also reduces the inspiratory volume [43–47].

Potential surgical risks are noted with the implantation of any foreign body, particularly given the vulnerability of these patients. In addition, technical failures in pacemaker implantation are possible, such as battery or receiver failure and antenna wire breakage. Systems are usually equipped with a low-battery alarm to prevent such events.

When using a respiratory pacemaker in pediatric patients, a characteristic complication may occur. Given that patients aged <15 years have high lung compliance, a paradoxical inward movement of the chest wall during negative pressure breathing can occur, which reduces significantly the volume of inhaled air. As compliance decreases after the age of 15 years and with an increase in time after spinal cord injury, chest excursion normalizes [18].

Electrical stimulation of the abdominal muscles

Transcutaneous (superficial) electrical stimulation of the abdominal muscles [called abdominal functional electrical stimulation (FES)] can cause contraction of the abdominal muscles even when they are paralyzed because of spinal cord injury [48].

Normally, exhalation is passive owing to the elasticity of the chest wall and lungs. Forced expiration and coughing involve the activation of the lower intercostal and abdominal muscles for normal cough generation. Since the abdominal muscles are usually partially or completely paralyzed in tetraplegia, patients with spinal cord injury are unable to clear their airways by coughing, which often results in respiratory complications such as atelectasis, pneumonia, and respiratory failure [9].

Abdominal FES is an effective method for improving respiratory function in these patients.

The technique represents a stimulation of obliquus externus abdominis and less often rectus abdominis muscles with electric current (Fig. 2). According to a previous study, the average maximum amplitude, average pulse width (pulse duration), and average stimulation frequency are 100 mA, 250 µs, and 50 Hz [49], respectively.

Cough is a key airway defense mechanism against respiratory complications. Patients with a peak cough flow (PCF) of >4.5 L/s have a lower risk of complications. Electrical stimulation of the abdominal muscles using electrodes on the skin causes a cough comparable to that which occurs with manual assistance [50]. According to a meta-analysis of four studies, abdominal FES statistically significantly increased the PCF in patients with spinal cord injury [standardized mean difference 2.43 L/s, 95% confidence interval (CI), 0.32–4.54] [49]. This immediate improvement in PCF should reduce the respiratory complications of tetraplegia. Abdominal FES is a direct-acting clinical tool that can be combined with conventional methods such as manual assistance in coughing, mechanical insufflation–exsufflation, tracheobronchial debridement, and postural drainage [49].

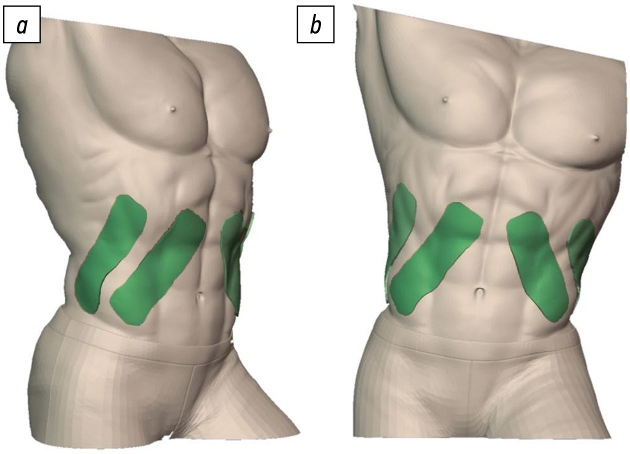

Fig. 2. Scheme of the posterolateral arrangement of electrodes during abdominal functional electrical stimulation: *a,* abdomen at an angle of 45°; *b,* abdomen in front view (areas of electrode application are marked)

Abdominal FES is an affordable noninvasive method to achieve functional improvements in cough and respiratory function and can provide an immediate effective cough in patients with tetraplegia. Daily abdominal FES for 6 weeks may improve respiratory function without assistance. In addition, repeated applications of this technique can reduce the duration of invasive ventilation and time of using a tracheostome. Abdominal FES was effective in patients with acute and chronic spinal cord injury [51].

The effective use of abdominal FES requires intact motor neurons. In patients with damage to motor neurons, flaccid paralysis occurred, and after injury, muscle atrophy quickly occurs; as a result, abdominal FES in such patients may be of little use.

Epidural stimulation

Epidural stimulation of the spinal cord below the level of traumatic injury can restore autonomic and volitional sensorimotor functions even in cases of clinically complete interruption of the spinal cord [2, 10–14, 52–55].

The activation of the inspiratory intercostal muscles is achieved by placing a single electrode on the ventral epidural surface at the Th_{II} level. In a clinical study of patients with ALV-dependent tetraplegia, the activation of the intercostal muscles alone increased the inspiratory volume from 470 to 850 mL in four of the five patients. However, the maximum duration of ventilation maintenance varied from 20 to 165 min [56]. Although the stimulation of the intercostal muscles results in a significant increase in inhaled air, this technique does not provide sufficient volume to maintain adequate ventilation for a long time.

Later, the concept of high-frequency (HF) epidural stimulation was proposed to activate the inspiratory muscles [57, 58].

HF (300 Hz) spinal cord stimulation (HF-SCS) through a single epidural electrode at the level of the thoracic vertebra II (Th_{II}) can induce a physiological pattern of inspiratory muscle activation in experimental animals with models of spinal cord injury [58].

Moreover, evoked potentials recorded during electromyography are similar to spontaneous physiological respiration [58].

HF-SCS may also be useful in restoring independence from ALV in patients with contraindications to respiratory pacemaker implantation [58, 59], i.e., with damage to the phrenic motor neurons at the level of C_{III}–C_V segments and/or to the phrenic nerves. To activate these respiratory muscles, temporary interference stimulation was employed [60]. Previous findings have been applied to the care of these patients [52, 61]. The presented data demonstrate the possibility of using epidural stimulation to the spinal cord with functional activation of the respiratory muscles and/or neuromodulation.

To activate the expiratory muscles, an effective cough mechanism was induced by stimulating the spinal cord in the lower thoracic and upper lumbar segments. Epidural electrodes were placed at the level of the vertebral bodies Th_{IX}, Th_{XI}, and L_I. Against HF stimulation, the main expiratory muscles contracted, the airway pressure reached 90 cm w.c. and 82 cm w.c. with stimulation of Th_{IX} and L_I, and the maximum expiratory flow rates were 6.4 and 5.0 L/s, respectively. With combined stimulation of Th_{IX} and L_I, airway pressure and expiratory flow rate increased to 132 cm w.c. and 7.4 L/s, respectively [52].

Thus, epidural stimulation represents a promising method for promoting respiratory neuroplasticity to achieve long-term respiratory rehabilitation. Given the described physiological effects, epidural spinal cord stimulation can restore diaphragmatic function and can be included in a modern rehabilitation strategy to restore independence from ALV and improve respiratory function in patients with spontaneous breathing following spinal cord injury.

Transcutaneous spinal cord stimulation

TCSS uses skin electrodes placed over the vertebrae to stimulate the spinal cord and provide motor control [62]. TCSS may be a viable alternative to epidural stimulation because it allows the re-engagement of spinal locomotor networks in patients with clinically complete spinal cord injury and facilitates voluntary control over generated stepping movements [63].

Computational models suggest that TCSS can activate similar spinal structures to modulate spinal cord excitability depending on specific parameters [64].

This technique has been evaluated quite well, and its efficiency in correcting locomotor function, increasing strength and volitional control of limb muscles has been confirmed [65–67]. Unfortunately, at present, no studies have analyzed large groups of patients using TCSS for the treatment of respiratory disorders; however, TCSS of the cervical spinal cord has shown promising results in terms of respiratory function and generating cough in patients with chronic spinal cord injury [68].

Dynamic changes in pulmonary ventilation and gas exchange parameters during the stimulation of Th_{XI}–Th_{XII} in 10 young men were assessed. The results revealed that the stepwise movement caused by TCSS increases the respiratory rate [69].

Thus, considering the positive experience of the effect of transcutaneous stimulation on various parts of the spinal cord and isolated cases of improvement in respiratory function in patients with chronic trauma, this technique can be a real approach to promote respiratory neuroplasticity, which certainly should be further evaluated. Moreover, the most effective schemes of stimulation should be selected considering the data obtained and experience in using invasive stimulation methods.

CONCLUSION

Currently, new treatment options have been developed for patients with tetraplegia, with reduced lung ventilation function. Many studies have shown the positive effect of electrical stimulation techniques on ventilation function such as a reduction in ALV time and number of infectious and other lung complications. Various treatment strategies have been described to improve respiratory function after spinal cord injury. Long-term courses of electrical stimulation contribute to the development of neuroplasticity, restructuring of neural circuits, improvement of respiratory function, and restoration of the ability of spontaneous breathing in these patients. Electrical stimulation is preferred over artificial ventilation and passive coughing methods. In addition, to invasive electrical stimulation of the phrenic nerve and/or spinal cord, less invasive electrical stimulation techniques need to be explored for use in patients with respiratory failure caused by spinal cord injury.

ADDITIONAL INFORMATION

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Author contributions. *V.G. Toriya* wrote all sections of the article, collected and analyzed the information analyzed the literature, and created the figures. *S.V. Vissarionov* performed staged and final editing of the text of the article. *M.V. Savina* and *A.G. Baindurashvili* performed staged editing of the article text.

All authors made a significant contribution to the study and preparation of the article and read and approved the final version before its publication.

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