Spinal Cord Stimulation to Restore Cough
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HUMAN INVESTIGATION PROTOCOL

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II. Title

Spinal Cord Stimulation to Restore Cough

III. Key Words

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IV. Abstract

Patients with cervical and thoracic spinal cord injuries often have paralysis of a major portion of their expiratory muscles and therefore, lack a normal cough mechanism.[1] Consequently, most of these patients suffer from a markedly reduced ability to clear airway secretions, a factor which contributes to the development of recurrent respiratory tract infections.[2,3] Since the spinal cord below the level of injury is intact in most patients, the motorneurons of the spinal cord and peripheral neuromuscular system innervating the expiratory muscles are intact. These muscles, therefore, can be electrically activated by electrical stimulation of the spinal roots to produce a functionally effective cough. Recent animal studies (performed in our laboratory) indicate that a major portion of expiratory muscles can be activated reproducibly and in concert by lower thoracic spinal cord stimulation (SCS). It is our hypothesis that lower thoracic SCS will result in the generation of large positive airway pressures and peak expiratory flow rates characteristic of a normal cough. This methodology, therefore, has the potential to produce an effective cough mechanism in

spinal cord injured patients. We plan to apply this technique to patients with spinal cord injury who have paralysis of a major portion of their expiratory muscles. Functional electrical stimulation of the expiratory muscles should be capable of producing an effective cough mechanism on demand and obviate the need for frequent patient suctioning which often requires the constant presence of trained personnel. Moreover, this technique should provide spinal cord injured patients the capacity to clear their secretions more readily and thereby reduce the incidence of respiratory complications and associated morbidity and mortality.

V. Description and Rationale

A. Background

Respiratory complications still account for most of the deaths in patients with spinal cord injury.[4] Despite intense respiratory management, these patients frequently develop atelectasis and bronchial pneumonia secondary to their inability to cough and clear secretions.[5] Lacking an adequate cough defense system occurs as a consequence of paralysis of virtually all their expiratory muscles.[6] Currently employed techniques to manage airway secretions include manual assistance by abdominal compression,[7] and/or use of a mechanical insufflation-exsufflation device.[8] While both methods have been shown to facilitate airway secretion clearance, they are dependent upon trained personnel and provider-patient coordination. Consequently, these methods are costly and labor intensive, often requiring the constant presence of trained personnel. Functional electrical stimulation of the expiratory muscles should be capable of producing an effective cough mechanism on demand and obviate the need for the frequent presence of trained personnel. This will allow spinal cord patients to clear secretions more readily, improve their lifestyle, and hopefully reduce the morbidity and mortality secondary to respiratory complications.

Conventional techniques for airway clearance. There are several different methods of airway clearance of secretions currently employed in the management of spinal cord injured patients who do not have a functional cough.[9] These include: A) Gravity. By this method, the patient is placed in the supine or prone posture with the head in a dependent position. The position of the body is rotated to allow secretions from different lobes of the lung to drain by gravitational effects alone. B) Active Suctioning. By this method secretions are cleared by inserting a catheter either through the naso-pharynx or tracheostomy to suction the airways with the use of a mechanical pump. This method is generally successful for removal of heavy secretions from the large airways. C) Assisted Cough. This method involves the application of external force to the abdominal wall, usually by a therapist or assistant. The patient rests in a reclining position, and the abdominal wall is compressed forcefully to increase abdominal pressure and, consequently, intrathoracic pressure to expel secretions.

Unfortunately, each of these methods has significant limitations which limit their effectiveness. The removal of secretions by gravity requires repositioning patients in relatively awkward positions for prolonged time periods and is quite uncomfortable. Active suctioning clears secretions from the large airways, but does not allow active removal of secretions from small airways where they are produced and often create

problems with gas exchange. Furthermore, this method can result in tracheal injury and irritation causing recurrent hemoptysis and patient discomfort. The assisted cough method can increase intrathoracic airway pressures to a small extent (10-15%). However, unlike natural cough production, this method does not result in uniform distribution of pressure within the intrathoracic cavity and, therefore, has limited effectiveness in many patients. In addition, this method is labor intensive requiring the assistance of a therapist to position the patient and perform the maneuver.

The deposition of material within the tracheobronchial tree occurs during various normal physical phenomena including inspiration, sedimentation, gas movement, turbulence and electrostatic forces.[10] Most secretions are usually removed by mucociliary activity which washes the mucus blanket of the airways above the trachea, functioning as a mucociliary escalator. This mechanism is quickly overwhelmed when secretions become excessive; in which case, cough becomes the primary means of secretion removal. For patients with spinal cord injury who lack an effective cough, active suctioning is usually required to remove secretions on a regular basis, usually several times per day.

Currently, therefore, there is no adequate method for achieving normal cough in this patient population. As a consequence, they suffer from the frequent development of respiratory complications, particularly respiratory tract infections.

2. Mechanisms of cough. The sequence of cough is grouped into four phases: inspiration, compression, expiration and cessation.[11] During the first phase, a variable amount of air is inhaled. The greater the amount of air inhaled, the larger the force developed by the expiratory muscles. During inspiration the intercostal muscles and diaphragm contract and increase the vertical and antero-posterior dimension of the chest. During the second, or compressive phase, glottic closure occurs. This event differentiates cough from other forced expiratory maneuvers. When the expiratory muscles contract against a closed glottis, intrathoracic pressures become quite high and may exceed 200 cm H_2O. When pleural pressure increases, lung volume decreases as intrathoracic gases are compressed. The glottis remains closed for approximately 200 msec. The third or expiratory phase occurs when the glottis opens. This is an active process associated with passive oscillations of tissue and gas. These oscillations cause a noise, which characterizes cough. Following glottic opening, intrathoracic pressure drops rapidly towards atmospheric levels, whereas the pressure at the alveolar level remains positive and actually continues to rise for a short while. The high interalveolar pressures simultaneously promote high expiratory flow rates and tend to collapse central airways. Accordingly, the transient peaks of expiratory flow noted during cough represent both the sum of the flow related to the displaced volumes of gas in the central airways which are dynamically collapsed and also the flow of gas from distal parenchymal units passing through these collapsing airways. The final phase is characterized by the antagonistic activity of the diaphragm and other inspiratory muscles and also relaxation of the expiratory muscles and the return to normal breathing.

Functional electrical stimulation of the abdominal muscles can be coordinated with voluntary efforts to reproduce this sequence of natural cough.[12]

3. Anatomy and function of the major expiratory muscles.

There are two major groups of expiratory muscles, the abdominal muscles and internal intercostal muscles, the former of which are most important.[13]

a) Abdominal muscles. There are four abdominal muscles that have significant respiratory function in humans.[14] These are the external oblique, internal oblique, transversus abdominis and the rectus abdominis. These muscles also have important functions as flexors and rotators of the trunk. As respiratory muscles, they have two principle actions. Due to the circumferential orientation of the internal and external obliques and transversus muscles, these muscles can push the abdominal wall inward and increase intra-abdominal pressure. Increases in intra-abdominal pressure force the diaphragm cephalad into the thoracic cavity. The other principle action of the abdominal muscles is to pull the rib cage downward. This is accomplished by the rectus and internal and external oblique muscles.

The external oblique is the most superficial muscle of the abdominal wall and arises from the last seven or eight ribs by a series of slips that fuse to form a broad muscle. These muscle fibers traverse forward and downward and form a broad aponeurosis as they insert in the midline. The external oblique is innervated by a branch of the subglossal and lower sixth intercostal nerves which innervate the muscle close to its origin. The internal oblique muscle lies immediately beneath the external muscle and is separated only by a small amount of fascia. Muscle fibers run upward at approximately right angles to the fibers of the external oblique. In essence, the fibers of the external and internal oblique muscles run at right angles to each other. The internal oblique is innervated by branches of the subcostal and last two intercostal nerves and often by fibers of the first lumbar nerve. The transversus abdominal muscle arises from the cartilage of the lower six ribs. These fibers run horizontally. Much of the transversus muscle is innervated by branches of the spinal nerves between T_4 and T_{12}. The rectus abdominis muscle is attached to the fifth, sixth and seventh intercostal cartilage and xiphoid process and extends down to the pubic crest. These fibers run perpendicular to the transversus abdominis muscle. This muscle is innervated by the terminal branches of the lower sixth or seventh thoracic nerves.

b. Internal intercostal muscles.

There are twelve pairs of internal intercostal muscles.[15] These muscles arise from the superior portion of the lower rib and insert on the inferior surface of the rib above. In the upper six interspaces (T_1-T_6), these muscles are extremely thin and have negligible capacity to produce changes in airway pressure. In the lower six interspaces (T_7-T_{12}), however, these muscles are quite thick and actively contribute to expiration.

We have recently shown that the transversus abdominis and oblique muscles are the major force generating muscles, with a smaller role played by the internal intercostal muscles.[16] The rectus abdominal muscle, in contrast, is responsible for only minimal pressure generation.

It should be noted that quiet respiration is characterized by passive relaxation of the lungs and chest wall. Forceful expiration, however, requires a coordinated contraction of the abdominal muscles, which act to compress the abdomen and facilitate expiratory airflow. Forceful contraction of the abdominal muscles occurs during cough, voluntary forced expiration, sneezing, and phonation.

The pressure generation-lung volume relationship of the expiratory muscles was previously examined in our laboratory in animal studies.[17] These studies indicate that the force generating capacity of the expiratory muscles is highly dependent upon lung volume. The pressure generated by the expiratory muscles increases progressively as lung volume increases and reaches maximum levels at total lung capacity, the point at which maximum spontaneous cough occurs.

4. Assessment of cough. Cough effectiveness can be assessed by measuring several different parameters including expiratory flow rate at the airway opening, maximum expiratory pressures, intrathoracic pressures and intra-abdominal pressures. Some indication of individual muscle performance can also be assessed by recording the EMG activities of these muscles.

5. Potential methods of expiratory muscle stimulation.

There are four potential methods by which the expiratory muscles can be activated to produce cough: 1) high-frequency magnetic stimulation, 2) surface abdominal muscle stimulation, 3) lower thoracic spinal cord stimulation, and 4) ventral root stimulation.

First, high frequency magnetic stimulation is currently an experimental device, which can be applied to the lower back to activate the neural pathways innervating the expiratory muscles. The major disadvantage of this device is that it is quite large, and therefore, not portable. Furthermore, this device requires a 220 V power source, and current applied at high frequencies (> 25 Hz), generates substantial heat at the stimulating coil and, consequently, carries the risk of thermal injury. This is a substantial disadvantage since quadriplegics, even ventilator dependent patients, are quite mobile and cough is often required on demand. Moreover, we have recently tested this device (High Speed Magnetic Stimulation; Cadwell Labs, Kennewick, WA) in animals and found that airway pressure changes were only approximately 40% of that produced by SCS.

A second potential method is direct stimulation of the abdominal muscles with electrodes positioned over the surface of the abdominal wall. There are only two brief reports of this method in the literature.[9,18] In quadriplegic patients, one study demonstrated that maximum expiratory pressure could be increased by approximately 30 cm H_2O during assisted cough to 55-60 cm H_2O. In comparison, a maximal cough effort in normal humans results in the generation of much larger positive airway pressures in the range of 200 cm H_2O or greater.[19] In a second study, also in quadriplegics, peak flow rates generated by surface electrical stimulation were quite modest and not significantly different than volitional cough. Moreover, no significant abdominal muscle contraction

could be elicited in more than 20% of patients.[9] The risks associated with high levels of electrical current applied to the skin and superficial nerves are also unknown and may be a limiting factor. In our own studies, we have employed this method in 6 spinal cord injured patients and confirmed that airway pressure generation can be increased by approximately 30 cm H_2O in some patients but found that high stimulus currents are required (90-100 mA). Consequently, 3 patients had skin irritation as evidenced by erythema and in one patient mild edema, following short-term (20 min.) intermittent use; and, minimal or no changes in airway pressure were achieved in 2 patients, both of whom had moderate degrees of abdominal adipose tissue. The added electrical resistance of fatty tissue most likely interferes with current spread to the abdominal muscles, precluding their activation.

Third, we have recently shown in animal studies that lower thoracic SCS results in activation of the abdominal and internal intercostal (IIC) muscles and the generation of large positive airway pressures (80-100 cm H_2O) and high peak flow rates (300 l/min.) at functional residual capacity (FRC), suggesting that this method is superior to surface abdominal muscle stimulation. A. This method involves the placement of disc electrodes (4 mm diameter) on the dorsal surface of the spinal cord via a hemilaminectomy incision. B. These electrodes can be connected to a radiofrequency receiver by a 9 volt battery. Expiratory muscle contraction can be triggered by the patient with either hand or head control.

The fourth method is direct electrical stimulation of each of the ventral roots innervating the major expiratory muscles (T_7-L_3). While quite tedious, this method is most likely to result in maximum expiratory muscle activation. There are several disadvantages, however, of achieving expiratory muscle activation via direct root stimulation using multiple electrodes compared to epidural SCS. From a surgical standpoint, electrode placement around multiple roots is technically more difficult and associated with much greater morbidity, whereas spinal cord electrodes can be applied with relative ease (as is currently being applied for upper thoracic SCS for intercostal pacing or dorsal column stimulation for control of pain and spasticity).[21] There is also significant risk of mechanical and electrical injury with electrodes in direct contact with neural tissue. Moreover, intermittent application of the stimulus paradigm required to activate the expiratory muscles by lower thoracic SCS is well below the threshold for neural injury.

B. Specific aims and hypotheses

The purpose of the present study is to assess the utility of spinal cord stimulation to provide large positive airway pressures and expiratory airflow and simulate cough. Restoration of an effective cough in spinal cord injured patients should reduce the incidence of atelectasis and respiratory tract infections and thereby reduce the high morbidity and mortality associated with respiratory complications in this patient population.

VI. Subject population

A. Number and description of subjects

Eighteen patients with spinal cord injury will be recruited for this study. The study group will be comprised of 3 groups, each with a different level of injury: a) 6 patients with high cervical spinal cord injury (C_1-C_4) and, consequently, ventilator dependent, b) 6 patients with low cervical spinal cord injury (C_4-C_8) and able to breathe spontaneously, and c) 6 patients with thoracic spinal cord injury.

B. Source and method of recruitment

Contact will be made via letter or phone call to potential research subjects made known to us through the assistance of the Spinal Cord Center at MetroHealth Medical Center, the General Clinical Research Center, and previously known subjects from other trials.

C. Service responsible for medical care

The physician currently responsible for each patient's care will continue to provide primary medical care. We plan to work closely with that physician in terms of the management of spinal cord stimulation.

D. Inclusion and Exclusion Criteria

Patients 18 years of age and older with spinal cord injury will be considered for this study. Exclusion criteria will include patients with significant cardiovascular disease or active lung disease such as patients with bronchitis or pneumonia, and patients with any form of cardiac pacemaker.

E. Special considerations for particular groups of subjects

Prisoners, minors, legally incompetent or unconscious patients, pregnant women, housestaff, students and CWRU employees will not be studied.

VII. Methods and procedures

A. General study design

A medical evaluation will include a review of the patient's medical file, obtaining a complete history and performance of a physical examination. Patients will be admitted to the hospital for initial testing, which will include measurements of spontaneous tidal volume, vital capacity and respiratory muscle strength as determined by maximum inspiratory and expiratory pressures. These are all routine pulmonary function tests. A chest x-ray, plain x-rays of thoracic and lumbar spine, MRI of thoracic and lumbar spine, and ECG will also be performed. Spinal cord disc electrodes and radiofrequency receiver (NeuroControl Inc., Cleveland, OH) will then be placed by Dr. Geertman in the operating room under sterile conditions. Stimulus parameters will be set very low initially, and gradually increased. The effectiveness of spinal cord stimulation will be assessed by measurements of airway and gastric pressure, expired volume, expiratory flow rate, and abdominal EMG recordings. It is anticipated that very small airway pressures and flows will be achieved initially due to muscle atrophy. The procedure will be considered successful, however, if we are able to demonstrate spread of current over the muscles of the upper and lower abdominal wall in association with the generation of positive airway and gastric pressures and high expiratory flows. Stimulus duration will be set at short periods, (2-3 sec. on, 8.0 sec. off) for 5 minute

periods, three times/day, to retrain the expiratory muscles. The full benefit of training usually requires a minimum of 6-8 weeks. Similar training periods are also necessary to optimize the function of other respiratory muscles.

B. Specific procedures

1. Assessment of Expiratory Muscle Force and Expiratory Flow Generation

Airway, intrathoracic (esophageal) and intra-abdominal (gastric) pressures will be assessed during lower thoracic spinal cord stimulation under conditions of airway occlusion. Expiratory airflow will be measured following the release of occlusion. Esophageal and gastric pressures will be measured with a nasogastric catheter (a quarter inch in diameter) inserted into the esophagus and stomach via the nose after application of topical lidocaine anesthesia to the nasal membranes. This catheter has been used previously in many studies by ourselves and others to assess the forces generated by the respiratory muscles. We have never observed any significant complications, nor are there any reported. The major complaint of the subjects is throat soreness following removal of the catheter; this usually resolves within hours. Nasogastric catheters are routinely placed in many ill patients. Use of this catheter, therefore, does not represent the institution of a new device.

2. Abdominal Muscle EMG Recordings

Recording electrodes will be placed percutaneously into the anterior portion of the abdominal muscles on the anterior abdominal wall. Stainless steel electrodes within 25 gauge needles will be inserted to record from the upper and lower portions of the external oblique. This technique is considered quite safe. There is no risk of pneumothorax since these electrodes are positioned over the abdominal wall. The electrodes will remain in place for no longer than a few hours and then removed completely. This procedure will be performed on no more than two occasions on each patient.

3. Spinal Cord Electrode Implant Procedure

This procedure will be performed by Dr. Takaoka, a staff physician in the Department of Neurosurgery at MetroHealth Medical Center. A hemi-laminectomy will be performed at the level of the T_9-T_{10} or T_{10}-T_{11} vertebral body. Disc electrodes (NeuroControl, Inc.) will be positioned on the dorsal surface at the T_9, T_{11}, and L_1 spinal cord levels. Based upon known current spread, stimulation at these sites should result in complete activation of the expiratory muscles. The disc electrodes will be connected to a radiofrequency receiver, which will be implanted subcutaneously over the anterior chest wall.

Since the expiratory muscles are, in all likelihood, considerably atrophied from disuse, we do not expect to achieve large positive pressures and expiratory flows initially. Recordings of abdominal muscle EMGs will be made to assess the spread of current to activate the expiratory muscles. We will assess the effects of stimulation of

individual spinal cord sites and in combination to evaluate the optimum site(s) of spinal cord stimulation for activation of the expiratory muscles.

C. Special Procedures

Application for an investigational device exemption (IDE) from the Food and Drug Administration is pending. The IRB will be notified of the approval date and number. No studies will begin until this has been received.

D. Time Schedule

Two weeks prior to surgery, the patient will either come to MetroHealth Medical Center as an out-patient for pre-operative testing or have the testing done at their place of residence. Patients will spend the next 6-8 weeks at the General Clinical Research Center for post-operative care followed by muscle reconditioning and recording of data. The entire process is expected to take approximately 3-4 months.

E. Method of data analysis.

The effects of stimulation at different stimulus sites alone and in combination will be compared in each patient. In addition, the effects of body position (upright, prone, and supine postures) on pressure generation and expiratory flow will be assessed. We expect that stimulation of specific electrode leads will result in maximal airway pressure and airflow generation.

Graphs will be constructed relating changes in stimulus amplitude (with stimulus frequency and pulse width fixed) to airway pressure generation and expiratory airflow. Likewise, changes in stimulus frequency and pulse width will be related to airway pressure and airflow while the other parameters are fixed.

Finally, the relationship between lung volume, airway pressure, and expiratory airflow will be determined utilizing optimal stimulus paradigms.

Statistical analysis will be performed using ANOVA and post hoc student t-tests. A p value < 0.05 will be taken as significant.

VIII. Safety of subjects and risk benefit status

A. Potential risks

Spinal cord stimulation is already in frequent use in patients with neuromuscular disorders and is considered a safe procedure.[22,23] Since some patients may have asymmetric injuries with some residual sensation below the level of injury, general anesthesia will be provided during surgery. The risks associated with the operative procedure are infection and loss of blood.

The stimulus amplitude necessary to activate the lower thoracic motor roots is higher than that currently employed in chronic spinal cord stimulation. In our own on-going clinical trial with upper thoracic spinal cord stimulation, we have not observed any significant adverse effects using stimulus parameters necessary to activate motor roots.[24] Upper thoracic spinal cord stimulation, however, is associated with mild contraction of the hand and straightening of the back. These movements, however, have been well

tolerated by each patient. Stimulus amplitude will be maintained below that which activates the lower extremities.

Dr. Takaoka, a staff member of the Department of Neurosurgery, has considerable expertise with this procedure, having performed this procedure routinely for several years. Pre and post-operative antibiotics will be given to minimize the risk of infection.

B. Precautions to minimize risks

Quadriplegic patients are known to suffer from a condition known as autonomic dysreflexia, a condition characterized by symptoms of headache, blotchy skin and sweating, high blood pressure and bradycardia. These symptoms can be triggered by SCS. We have observed these symptoms in only one of nine patients with upper thoracic SCS, during repetitive stimulation 12x/min., 12 hrs/day. Reduction in stimulation current prevented the occurrence of these symptoms. We plan to carefully monitor patients for the development of autonomic dysreflexia during lower thoracic SCS. We do not expect this to be a significant problem since stimulation will only be provided for brief periods (5 min.), 3 x a day.

C. Toxic/hazardous substances

Not applicable.

D. Radiobiolical information

Not applicable.

E. Potential benefits

Lower thoracic spinal cord stimulation may provide patients suffering from spinal cord injury a means of producing an artificial cough, thereby, reducing the chance of pneumonia, decreasing the number of hospitalizations, and reducing both morbidity and mortality.

IX. Significance

Many spinal cord injured patients suffer from recurrent atelectasis, respiratory tract infections, including bronchitis and pneumonia and significant discomfort due to the inability to clear respiratory secretions and foreign bodies. Since conventional methods to remove secretions are tedious, labor intensive and oftentimes largely ineffective, respiratory complications remain a major cause of morbidity and mortality in this patient population.

Lower thoracic SCS may provide a means of generating large airway positive pressures and expiratory airflows sufficient to mimic a normal cough. Restoration of cough may help reduce the incidence of respiratory complications and possibly improve both the life quality and longevity of spinal cord injured patients. Obviously, subsequent studies will be necessary to evaluate the potential benefit of this method in the clearance of airway secretions and foreign bodies.

X. Informed consent

The protocol will be explained to each patient by one of the investigators with the informed consent form provided. The patient will sign the consent form if he or she agrees to

participate in the study with full understanding of the purpose, risks and benefits of this research.

Advertising will not be used at this time.

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