Spinal Cord Stimulation with Wire Leads to Restore Cough

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HUMAN INVESTIGATION PROTOCOL

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II. Title

Spinal Cord Stimulation with Wire Leads to Restore Cough

III. Key Words

- spinal cord injury
- paralysis
- cough
- cervical spinal cord injury
- thoracic spinal cord injury

IV. Abstract

Respiratory complications account for significant morbidity and mortality in persons with spinal cord injury (SCI) due to their inability to cough and clear secretions. Consequently, they are dependent upon caregiver assistance for the application of manual suctioning, assisted coughing maneuvers or other methods of airway management. These methods are cumbersome, generally uncomfortable and require trained personnel. These individuals lack an effective cough mechanism due to paralysis of their expiratory muscles. Since the spinal cord below the level of injury is intact in most subjects, the motoneurons of the spinal cord and peripheral neuromuscular apparatus remain functional. Therefore, the expiratory muscles are amenable to functional electrical stimulation techniques. In a single site, pilot study of 16 tetraplegics, we have recently shown that the expiratory muscles can be electrically activated by spinal cord stimulation (SCS) to restore an effective cough, a method which involves the surgical placement of disc electrodes through laminotomy incisions. We demonstrated that this method is successful in achieving an effective means of expiratory muscle activation, as demonstrated by the generation of large positive airway pressures and expiratory airflow rates. Importantly, this technique facilitates secretion removal, reduces the need for caregiver support, reduces the incidence of respiratory tract infections and improves life quality. While successful, electrode placement requires an invasive and costly procedure. Consequently, many individuals were unwilling to pursue this technique. Based upon the results of animal and human studies, it is our

hypothesis that comparable activation of the expiratory muscles can be achieved with wire leads which can be inserted percutaneously through a needle, eliminating the need for the invasive laminotomy procedure and can be performed on an out-patient basis. This latter procedure would significantly shorten surgical time, lessen the degree of surgery, shorten recovery time, reduce costs, and thereby, increase patient and physician acceptance of this technique. The efficacy of SCS with wire leads will be assessed in 16 subjects with SCI, in terms of the capacity of this method to activate the expiratory muscles, restore an effective cough mechanism and achieve significant clinical benefits related to secretion management. Given the significant heterogeneity of this orphan population, subjects will serve as their own controls to evaluate the success of this technique. If successful, the wire lead system will provide a minimally invasive method of restoring cough and has the potential to significantly improve life quality. Ultimately, restoration of an effective cough with SCS has the potential to significantly improve the morbidity and mortality associated with respiratory complications in persons with SCI. This study will also provide the data necessary for a multi-center trial of this technique leading to eventual FDA approval.

Primary Aims:

1. Determine the utility of lower thoracic SCS with wire leads to produce large positive airway pressures and high peak expiratory airflow rates characteristic of an effective cough mechanism.

2. Evaluate the capacity of this technique to provide an effective means of clearing airway secretions, reduce the need for caregiver support, reduce the incidence of respiratory tract infections and improve subject quality of life and caregiver burden in subjects with cervical SCI.

Secondary Aims:

1. Determine if the use of wire leads for restoration of cough has greater appeal to patients with SCI and is associated with less risk and cost compared to the current method of SCS to restore cough.

2. Determine if the information from this study provides the necessary data to perform a multi-center trial and obtain FDA approval of this device.

V. Description and Rationale

Problem.

Respiratory complications still account for most of the morbidity and mortality in traumatic spinal cord injury (SCI) during the acute phase and also during later years. Despite intensive respiratory management, these patients frequently develop atelectasis, bronchitis and pneumonia. In epidemiological studies of over 5,000 patients sustaining SCI, the leading cause of death was pneumonia.[3] In fact, patients with SCI are ~150 times more likely to die from pneumonia compared to the general population.[17] The development of respiratory complications in SCI is directly related to the inability of these patients to cough and clear secretions. The lack of an adequate cough defense system occurs as a consequence of paralysis of virtually all of their expiratory muscles. Currently employed techniques to manage airway secretions include active suctioning, manual assistance by abdominal compression and/or use of a mechanical insufflation-exsufflation device. Each of these methods requires provider-patient coordination and is costly and labor intensive, requiring the constant presence of trained personnel. Moreover, despite use of these various modalities, respiratory complications continue to have a major

impact on the overall health and quality of life of patients with SCI. Functional electrical stimulation of the expiratory muscles has the potential to provide a more normal and effective cough mechanism.

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. 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 nasopharynx 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. 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.

Innovation

There are three potential methods by which the expiratory muscles can be activated to produce cough: 1) high-frequency magnetic stimulation (MS), 2) surface abdominal muscle stimulation (SS) and 3) lower thoracic SCS. First, MS is an experimental device which can be applied to the lower back to activate the neural pathways innervating the expiratory muscles. While this technique has the important advantage that it can be applied non-invasively, previous studies evaluating this technique in tetraplegic patients did not demonstrate significant increases in airway pressure generation. Moreover, this method has significant limitations including the generation of substantial heat at the stimulating coil and associated risk of thermal injury and lack of portability. With SS, substantial airway pressures can be generated with electrodes with very large surface areas. However, as with MS, this method carries the risk of thermal injury, skin irritation and breakdown. Finally, we have previously shown that SCS using disc electrodes results in activation of the expiratory muscles and the generation of large positive airway pressures and high peak expiratory airflow rates, in the range of those observed during a

maximal cough effort in normal individuals. In contrast to MS and SS, this device is portable, does not require the repeated application of electrodes to the body surface, thereby avoiding potential skin injury, and is more likely to be effective in all patients, even obese individuals. Unfortunately, disc electrode placement requires a costly and invasive procedure significantly limiting general application. It should be emphasized that this technology is not commercially available. Wire leads have been in clinical use for several decades for control of pain and spasticity using a minimally invasive surgical procedure allowing for significant clinical advantages over disc electrodes. Based upon our extensive studies in animals and temporary, intra-operative placement of wire leads in humans, we have determined that SCS to restore cough can be accomplished with wire leads in a parallel arrangement.

Specific aims and hypotheses

The purpose of the 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 (SCI) 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.

Hypothesis, therefore, that spinal cord stimulation (SCS) with wire leads, which can be inserted via minimally invasive techniques can a) be applied safely without the development of neural injury, b) result in sufficient activation of the expiratory muscles in persons with SCI to produce an effective cough mechanism, and c) have a significant clinical impact related to secretion clearance on subjects with SCI.

VI. Subject population

Number and description of subjects
We plan to evaluate 16 subjects of either sex. No subject will be excluded on the basis of race, religion or ethnic background. No pregnant women, children, prisoners, unconscious or incompetent people will be eligible.

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.

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.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Cervical spinal cord injury (C8 level of higher)
- 12 months post-injury (if AIS incomplete) or 6 months post-injury (if AIS complete)
- Expiratory muscle weakness (maximum expiratory pressure < or equal to 30% predicted normal value)
- 18 - 75 years old
- Determined by the surgical team to be an appropriate surgical candidate

- Adequate oxygenation (oxygen saturation > or equal to 90% on < or equal to 4 lpm supplemental oxygen)

Exclusion criteria:

- Untreated lung, cardiovascular or brain disease
- Minor infection at the site of implantation requiring antibiotics within the past 3 weeks
- Serious infection requiring hospitalization within the past 6 weeks
- Severe scoliosis or other chest deformity
- Marked obesity (body mass index > 50)
- Unmanaged hypertension or hypotension
- Low oxygenation (oxygen saturation < 90% on < or equal to 4 lpm supplemental oxygen)
- Pregnant or breast feeding

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

General study design

Preliminary Assessment

Prior to surgery, a history and physical examination will be completed. The following laboratory studies will be obtained: complete blood count with differential; comprehensive metabolic panel, which includes glucose, blood urea nitrogen, creatinine and calcium, total protein and albumin; prothrombin time, partial thromboplastin time and INR; and urinalysis with urine culture and sensitivity. A standard 12-lead electrocardiogram and chest x-ray will be obtained. MRI of the thoracic and lumbar spine and plain x-ray of the thoracic and lumbar spine may also be performed, unless contraindicated due to an existing condition. In the event an MRI cannot be performed, a CT myelogram is a suitable substitute. Significant abnormalities in any of these tests may interfere with the potential efficacy of SCS and, therefore, preclude surgery. Baseline spirometry will be measured utilizing standard equipment. Respiratory muscle strength will be assessed from measurements of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using a digital meter. The best of 3-5 efforts will be used. Predicted normal values will be calculated using NHANES III 1999 for spirometry and Enright 1995 for maximal respiratory pressures.

Surgical Procedures

In the operating room at MetroHealth Medical Center, Dr. Tabbaa (staff anesthesiologist) and/or Dr. Geertman (staff neurosurgeon) will perform the implantation of the spinal cord wire leads (Ardiem, Inc; Indiana, PA) and radiofrequency receiver (Finetech Medical; London, England). A separate member of the anesthesiology team will be present to monitor hemodynamic and ventilatory status. Patients will receive moderate IV sedation, which is the clinical standard for the implantation of epidural wire leads. The subjects will be placed in the prone posture with a pillow placed beneath the hips, prepared and draped. Under fluoroscopic guidance, the L1-L2 interspace will be identified. One and one-half vertebral levels caudal and lateral to the midline, the skin will be infiltrated with lidocaine 1% with bicarbonate using a 25-gauge needle. An incision will be made to the depth of the subcutaneous fascia and a size 14-gauge Tuohy needle will be inserted into the epidural space until resistance is met. Needle location will be confirmed under fluoroscopy. After rotating the needle so that the beveled edge faces cephalad, the needle stylet will be removed. For the second wire lead, a second needle will be placed, following the same steps as above, at an equal distance from the midline but to the right of the midline and approximately

one vertebral space below the first needle. The guide wire will be inserted through the first needle and advanced 1-3 cm past the needle tip. After removing the guide wire, the wire lead will be inserted through the needle, under fluoroscopic guidance, and advanced until the superior electrode contact is positioned at the T9 level just left of the midline. The second lead wire will be then be inserted to the right of midline, following the same steps just described, and advanced to the T9 spinal level. After verifying lead position using fluoroscopy, the needles will then be removed. Each wire lead will be secured with an anchor. A separate ground electrode will be implanted in a pocket over the paraspinal muscles. The lead wires will be tunneled to the mid-axillary area. The lead incision sites are then closed. The subject will then be placed in the lateral decubitus position and an incision will be made over the abdomen or lower chest to make a subcutaneous pocket. The radiofrequency receiver, identical to the receiver used in our recent clinical trial, will be placed in the pocket. Each lead wire will be connected via a connector receptacle to the receiver. The fascia and the subcutaneous tissue are then closed. In this protocol, the entire system will be implanted during a single procedure. SCS will be applied to each lead intra-operatively to verify electrode position. As with any surgical procedure, the subject will then be observed in the Recovery Room and, when stable from a hemodynamic and respiratory standpoint, admitted to a general medical ward (or telemetry unit for subjects with sleep apnea). Routine post-operative surgical care will be provided. The subject will be monitored for any signs of bleeding or infection. The subject is expected to be discharged the next day.

The potential complications of this procedure include infection and bleeding. The incidence of each of these is generally considered to be less than 1%. Dr. Tabbaa has performed parallel wire lead placement routinely for other indications of SCS for more than 20 years.

Postsurgical assessment
Participants who live outside of the Cleveland area will be required to stay in Cleveland for 10 to 14 days after discharge for a postsurgical assessment at the MHMC by Dr. Robert Geertman or a member of his team. This required stay could be extended if deemed necessary by Dr. Geertman or his surgical team for an unknown period of time.

Specific Physiologic Measurements
Airway pressure and peak expiratory airflow rate measurements during hospital out-patient visits.
Approximately 3-4 weeks after implantation of the SCS system, all subjects will return to the hospital for the initial application of electrical stimulation on an outpatient basis. At this time, cardiac rate and rhythm, oxygen saturation, and blood pressure will be monitored. All measurements will be made in the sitting posture. Airway pressure and peak expiratory airflow rate will be measured (connection will be made either with a facemask or tracheostomy tube), with a Biopac Data Acquisition System (Biopac Systems MP100).
- Airway pressure. Changes in airway pressure during expiratory efforts are reflective of the pressure developed within the major airways and will be used as an index of the force of expiratory muscle contraction. Prior to SCS, the subject will be asked to relax completely to assure absence of respiratory muscle activation. SCS will be applied for 0.6-0.8s during which time airway pressure will be recorded during airway occlusion.
- Expiratory airflow rate. Peak expiratory airflow rate is also a useful index of cough efficacy and will be monitored in each subject. Inspired and expired volume will be obtained by integration of the airflow signal. Peak expiratory airflow rate will be measured during SCS following release of occlusion.
- Effects of lung volume changes. Airway pressure generation will be assessed at both FRC and TLC. SCS will be applied at each of these lung volumes while measurements of airway pressure and peak expiratory airflow rates are made by the methods described above.
Measurements will also be made with the subject making their own expiratory effort in synchrony with activation of the expiratory muscles by the stimulation system. The subject will be asked to exhale forcefully against an occluded airway in synchrony with muscle activation during which time airway pressure and peak expiratory airflow rate will be monitored. This is the prescribed pattern of use of the system at home by the subject in order to cough and clear their airways.

Assessment of Clinical Outcome Parameters
The incidence of acute respiratory tract infections over a 2-year period will be collected prior to implantation of the study device. Following implantation, this will be tracked continually. Responses to questionnaires (life quality, caregiver burden and secretion management index) will be compared prior to implantation and also at defined endpoints during the study. Mean changes of each parameter for the entire group will be determined.

Method of data analysis
Graphs will be constructed relating changes in stimulus amplitude to airway pressure generation and expiratory airflow. Each of the subjects will serve as their own control. Upon overall significance, appropriate pairwise comparisons will be performed. Since these contrasts are equivalent to multiple t-tests between levels, protection against type I error will be accomplished with a Bonferroni correction. A p value of < 0.05 will be taken as indicating statistical significance. Statistical significance, however, does not necessarily translate into clinical significance.

VIII. Safety of subjects and risk benefit status

Potential risks

1. Pre-surgical Risks
Standard procedures will be performed prior to implantation of the investigational device to assure that the subject is appropriate for enrollment in the study and able to tolerate the surgical procedures. No experimental procedures will be performed during this period. Standard blood draws will be made for laboratory analysis. When blood is drawn from a vein, there will be some temporary discomfort and the minimal risk of local bruising, infection or blockage of the vein. Rarely, fainting occurs. Risks associated with radiation exposure may be related to the cumulative number of CT scans and other types of X-rays over a long period. Because the MRI machine functions as a large magnet, it could move iron-containing objects in the MRI room during the examination that could cause harm. Having a MRI may also cause some discomfort including claustrophobia and noise.

2. Surgical Risks
The surgical procedures will be performed by Dr. Tabbaa, staff physician in the Department of Anesthesiology and/or Dr. Geertman, staff physician in the Department of Neurosciences, both at MetroHealth Medical Center. Dr. Tabbaa has performed parallel wire lead placement routinely for other indications of SCS for more than 20 years. Dr. Geertman has implanted the study device in all 17 of our participants in our previous clinical trial using disc electrodes. All aspects of the surgical procedure are standard. However, the application of the wire leads for the purpose of expiratory muscle stimulation is experimental. The surgical procedures are expected to last 2 hours. Any surgical procedure carries a risk of infection and bleeding. The incidence of infection and excessive blood loss related to this surgery are generally considered to be less than 1%. Although unlikely, there is also a chance that the body will reject the implanted materials which will require their removal. It is possible to develop a pocket of fluid (seroma) around the receiver, and, if infected, the receiver will have to be removed. There is also a rare possibility that the stitches holding the leads and receiver in place will break causing these to shift in position. Other potential risks include lead migration and leakage of cerebrospinal fluid.

3. Risks Associated with Spinal Cord Stimulation
Tetraplegic 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. In our recent clinical trial, these symptoms occurred in ~ 20% of subjects and subsided quickly with discontinuation of stimulation. There is a remote possibility that bowel or bladder discharge

will occur due to contraction of the abdominal muscles during stimulation. Of note, there has been no occurrence of this potential complication in our recent clinical trial using disc electrodes for SCS. Some leg movement may occur with T11 stimulation. In our recent clinical trial, this was well tolerated in each subject. Due to improper use of the external transmitter (i.e. maintained in place continuously for days and weeks with tight fitting clothing), the receiver may erode through the skin exposing the subject to the risk of infection. There is the remote possibility of electrically induced tissue damage. This is unlikely since the ranges of stimulus amplitude and pulse width are known to be safe. Moreover, the duration of stimulation is very brief. It is possible that placement of the device may worsen spasticity after implantation. This is rare and may ultimately require removal of the device. Temporary or transient sensory changes, such as electric like sensations, may be present during stimulation. These are uncommon and well tolerated, but can be lessened with changes in the stimulation parameters.

4. Device Malfunction
The most common cause of device malfunction is decoupling of the external transmitter over the implanted receiver. Low battery power can also result in device malfunction. An error on the control box will display if there is low battery power. The battery charge status can be checked at any time on the control box. The occurrence of fibrosis at the electrode-tissue interface could affect the long-term physiologic performance of the device. These damages were not encountered in our recent clinical trial nor highly anticipated since the implanted materials are biologically inert.
Improper activation of the implanted receiver could occur by external sources other than the subject's transmitter. However, this is unlikely since the external transmitter must be placed close to the implanted receiver to power the device.

Precautions to minimize risks
1. Pre-Surgical
During standard blood draws, suitable precautions will be taken to minimize risks of bruising, infection or blockage of the vein.
Because MRI could result in movement of iron-containing objects, precautions will be taken to minimize such events. Loose metal objects, like pocketknives or key chains, will not be allowed in the MRI room. Earplugs will be applied to prevent temporary hearing loss.

2. Surgical
While the incidence of infection and excessive blood loss related to this surgery are generally considered to be very low, every effort to minimize this risk will be taken before, during, and after the procedure, including administration of antibiotics.

3. Spinal Cord Stimulation
Given the possibility of autonomic dysreflexia in response to SCS, blood pressure and pulse will be monitored closely during hospital out-patient visits and at home during the initial period of SCS. If significant blood pressure changes occur (systolic > 140 mmHg) during SCS or if the subject experiences symptoms of autonomic dysreflexia (AD), stimulation will be stopped until hemodynamic parameters stabilize. Based upon our previous experience, increasing the interval between applied SCS minimizes hemodynamic changes and when signs of AD occur initially, they eventually resolve completely over the subsequent 3-4 weeks such that stimulation can be provided very frequently without untoward effects. However, if signs or symptoms of AD persist, Clinical Practice Guidelines of the Consortium for Spinal Cord Medicine for management of AD will be followed. If necessary, the study will be discontinued.
Given the potential of erosion of the receiver through the skin, the subject's skin will be inspected daily for redness and/or irritation and any abnormalities immediately reported to the study team. The subject and caregiver will be instructed to remove the external transmitter each night, inspect the skin and immediately report any abnormal findings to the study team.

4. Device Malfunction
To prevent decoupling of the external transmitter over the implanted receiver, the subject and caregiver will be provided specific instructions on proper application of the device. Methods to assure maintenance of adequate battery power will also be provided, including instruction on how to check the status of battery charge. The level of applied electrical stimulation will be maintained within specific parameters that are known to be safe and not result in deleterious side effects.

Toxic/hazardous substances
Not applicable

Radiobiolical information
Not applicable

Potential benefits
Based upon our recent clinical trial, lower thoracic spinal cord stimulation using disc electrodes results in near maximal expiratory muscle activation, as reflected by the generation of large airway pressures and expiratory airflow rates in the range of those achieved with a maximum cough effort in normal persons. More importantly, this technique is a highly effective method of secretion clearance as it significantly reduces the difficulty in raising secretions and the need for caregiver support, reduces the incidence of respiratory tract infections and improves life quality. Subjects also reported that this method is far more portable and comfortable compared to previously used methods of secretion management.

It is our hypothesis that an effective cough can be achieved with SCS using wire leads, which can be placed by a much less invasive surgical procedure. If successful, this technique will have greater appeal to persons with SCI and be associated with less risk and cost while achieving the same clinical benefits. Moreover, this technique has the potential to reduce the high morbidity and mortality associated with respiratory complications in this population.

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.

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.