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High Frequency Spinal Cord Stimulation – New Method to Restore Cough

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Abstract

Spinal cord stimulation (SCS, 50Hz) is a useful method to restore an effective cough in persons with spinal cord injury (SCI). However, high stimulus amplitudes and potential activation of pain fibers, significantly limits this application. It is our hypothesis that high frequency SCS (HF-SCS), with low stimulus amplitudes may provide the same level of expiratory muscle activation. In 6 dogs, the effects of SCS, with varying stimulus parameters on positive pressure (P) generation was evaluated. At any given level of stimulus current, mean P was largest at 500Hz, compared to all other stimulus frequencies. For example, with stimulation at 1mA and frequencies of 200, 500 and 600Hz, P were 25±3, 58±4, 51±6cmH₂O, respectively. By comparison, P achieved with conventional SCS parameters was 61±5cmH₂O. HF-SCS results in a comparable P compared to that achieved with conventional stimulus parameters but with much lower stimulus amplitudes. This method may be useful to restore cough even in subjects with intact sensation.

Keywords

Expiratory Muscles; Spinal Cord Stimulation; Cough; Rehabilitation

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1. Introduction

In patients with neuromuscular diseases, including spinal cord injury (SCI), stroke, and amyotrophic lateral sclerosis, expiratory muscle weakness and the inability to generate an effective cough and clear secretions are a major cause of respiratory complications including bronchitis and pneumonia. In fact, pneumonia is a common cause of death in these patient populations (Corcia et al., 2008, DeVivo et al., 1999, Zhang et al., 2014). In a recent human clinical trial in subjects with SCI, we demonstrated that lower thoracic spinal cord stimulation (SCS, 50Hz) results in activation of the expiratory muscles and the generation of large positive airway pressures and high peak airflow rates characteristic of a normal cough (DiMarco et al 2006, 2009a, 2009b). Restoration of an effective cough resulted in greater ease in raising secretions, reductions in the incidence of respiratory tract infections, and improvement in life quality DiMarco et al., 2009b. Unfortunately, activation of the respiratory muscles via this technique requires high stimulus amplitudes (30–40V), and therefore cannot be applied in subjects with intact sensation, as stimulation would result in significant discomfort due to sensory fiber activation.

In prior studies utilizing HF-SCS applied to the upper thoracic SCS to activate the inspiratory muscles, we demonstrated that electrical stimulation with stimulus frequencies in the range of ~300 Hz with low currents (~1–2 mA) results in very large inspired volumes approximating the inspiratory capacity (DiMarco and Kowalski, 2009, 2013). Our results suggested that upper thoracic HF-SCS results in activation of the phrenic and intercostal motoneuron pools allowing processing of the signal, and the activation of the inspiratory muscles at physiological firing frequencies. We postulated that the motoneurons of the lower thoracic spinal cord could also be activated in similar fashion at the appropriate stimulus frequencies.

In the present study, we demonstrate in animal testing that expiratory muscle activation can also be achieved with SCS utilizing very low stimulus amplitudes (<2mA) but with high stimulus frequencies (400Hz). It is our hypothesis that lower thoracic HF-SCS will result in sufficient activation of the expiratory muscles to provide large positive airway pressures necessary to generate an effective cough. Restoration of an effective cough may allow patients with various neuromuscular disorders to effectively clear secretions and reduce the morbidity and mortality associated with respiratory complications.

2. Methods

Studies were performed on 6 mongrel dogs weighing 24.9 to 29.0kg (mean: 26.3 ± 0.6 kg). All animals were anesthetized with pentobarbital sodium. An initial dose of 25mg/kg was given intravenously; additional doses of 1 to 2mg/kg were provided, as needed. Animals were tracheostomized and intubated with a cuffed endotracheal (10mm ID). A catheter was placed in the femoral vein to administer fluids and supplemental anesthesia. A second catheter was placed in the femoral artery for continuous monitoring of blood pressure and heart rate (Waveline Pro Multi-Function Monitor, DRE Inc., Louisville, KY). Body temperature was maintained with a heating blanket (Harvard Apparatus, Cambridge, MA) at $38 \pm 0.5^\circ\text{C}$. Airway pressure generation during SCS was measured at functional residual

capacity (FRC) following airway occlusion with a pressure transducer (Validyne, MP45, Northridge, CA) connected to the airway opening.

A laminectomy was performed at the T7 level to allow placement of an eight plate stimulation lead with 4mm contacts (model AD-TEDH Medical Instrument Corp, Racine, WI), which was advanced to the T9 level on the dorsal surface of the spinal cord. An indifferent ground electrode was implanted in the back musculature. A Grass square-wave pulse stimulator (model S88, Grass Technologies, West Warwick, RI) equipped with a stimulus isolation unit (PSIU6, Grass Technologies) was used to provide monopolar electrical stimulation over a range of stimulus frequencies (0–1,000Hz) and stimulus amplitudes (0–15mA). Stimulus train duration was fixed at 1.2s since a plateau in pressure generation is generally achieved by this time.

EMG recordings of the external oblique (*just below the costal margin*) were assessed with use of bipolar teflon-coated, stainless steel fine-wire electrodes, uninsulated at their terminal ~5mm. Changes in airway pressure generation and EMG activity were assessed during SCS over a wide range of stimulus currents (0.5–15mA, 0.2ms pulse width). Stimulus amplitude was limited to 2mA since higher currents resulted in significant reductions in pressure generating capacity and therefore have no practical application. At each level of stimulus current, the effects of changes in stimulus frequency were assessed (between 50–800Hz).

Data Analysis

Curves were constructed relating stimulus current to airway pressure generation at fixed stimulus frequencies of 50, 100, 200, 300, 500, 600 and 800Hz. Comparisons were made, where applicable, using repeated measures ANOVA and post-hoc Newman-Keuls tests. A p value <0.05 was accepted as statistically significant. Data are reported as mean $\pm$ SE.

3. Results

Effects of SCS on expiratory muscle activation and airway pressure generation

Comparison of low frequency (50Hz) spinal cord stimulation (LF-SCS) and high frequency (500Hz) spinal cord stimulation (HF-SCS) applied at the T9 spinal level on electromyographic (EMG) activities from the external oblique muscle (middle portion at the T13 spinal level) and airway pressure generation as a function of stimulus amplitude are shown in Fig. 1. In Fig. 1A, raw data from one animal is presented in which the effects of 50Hz stimulation (upper panel) vs. 500Hz stimulation (lower panel) on airway pressure generation are compared. At any given level of stimulus current below 2mA, airway pressure generation was substantially larger at 500Hz compared to 50Hz. For example, with stimulus current at 1mA, airway pressures were 60cmH₂O and 11cmH₂O with 500 and 50Hz, respectively. To achieve an airway pressure of 60cmH₂O with 50Hz stimulation, much larger current (15mA) was required. As shown in Fig. 1B, mean airway pressure generation during LF-SCS (50Hz, 15mA) was not significantly different than that achieved with HF-SCS (500Hz, 1mA) (61 ± 5 cmH₂O vs 58 ± 4 cmH₂O, respectively $p>0.05$).

Mean airway pressure generation as a function of stimulus amplitude (0.2ms pulse width) at various stimulus frequencies is shown in Fig. 2. At each applied stimulus frequency, airway

pressure generation increased with increasing stimulus amplitude from 50 to 500Hz. Maximum airway pressure was generated at 500Hz with 1mA stimulation ($58 \pm 4\text{cmH}_2\text{O}$). Stimulation with stimulus frequencies greater than 500Hz did not result in further increases in airway pressure generation. Rather, airway pressure generation decreased with the application of stimulus frequencies greater than 500Hz. With conventional stimulus frequencies (50Hz) however, airway pressure generation was substantially smaller than that achieved with stimulus frequencies $\geq 200\text{Hz}$ at all stimulus amplitudes.

4. Discussion

These preliminary findings indicate that large airway pressures comparable to those achieved with LF-SCS can be achieved with HF-SCS but with very small current requirements. These results have important clinical implications as they suggest that HF-SCS may have application to restore an effective cough in non-SCI population groups with intact sensation.

4.1. Comparison to current method of expiratory muscle activation via LF-SCS

In our previous animal investigation with high stimulus amplitudes (15mA) and 50Hz stimulus frequencies applied in the same spinal region (T9), we demonstrated, that SCS results in direct activation of spinal roots in the vicinity of stimulating electrode and more distal motor roots via spinal cord pathways (DiMarco et al., 1999, 2002). This demonstration was accomplished by evaluation of the latencies of compound action potentials of motor roots at various spinal cord levels (DiMarco et al., 1999). With high stimulus currents (15mA), only motor roots within two to three spinal segments rostral and caudal to the stimulating electrode were activated by direct stimulation (short-latency responses). More distal motor roots were activated via spinal cord pathways (long-latency responses). Following sequential spinal cord section, we also determined that dorsal column section had the greatest impact on pressure generation during HF-SCS, suggesting that pathways in this region of the spinal cord were the major pathway of activation of more caudal motor roots (DiMarco et al., 2002). We have subsequently applied this method in a clinical trial and demonstrated that an effective cough could be restored in spinal cord injured subjects with no residual sensation over the lower rib cage and abdominal wall (DiMarco et al., 2006, 2009a, 2009b).

4.2. Mechanism of expiratory muscle activation via HF-SCS

The mechanism by which the expiratory muscles are activated by the application of the HF-SCS in the region of lower thoracic spinal cord is not clear. If similar to HF-SCS of the upper thoracic spinal cord, which causes in activation of the inspiratory muscles, this method described herein causes activation of expiratory motoneurons rather than motor roots (DiMarco and Kowalski, 2009, 2013). Whether expiratory motoneurons are activated directly or via a spinal network is uncertain. Further studies will be necessary to evaluate the specific pathways by which the expiratory muscles are activated. This information would allow determination of optimal electrode placement and minimization of the amount of injected current.

4.3. Potential clinical application

HF-SCS is a unique method which could theoretically be applied in patient populations who would benefit from restoration of an effective cough, including stroke and amyotrophic lateral sclerosis, who have intact sensation. Future animal studies, will be necessary to resolve important basic science issues concerning this method, in advance of clinical trials.

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HIGHLIGHTS

- HF-SCS with low stimulus amplitudes causes marked expiratory muscle activation
- HF-SCS results in the generation of large airway pressures typical of a normal cough
- This method may be an important clinical tool for restoration of an effective cough

Fig. 1.

A - Comparison of 50Hz (LF-SCS) and 500Hz (HF-SCS) stimulation applied at the T9 spinal level on electromyographic (EMG) activities from the external oblique muscle (middle portion at the T13 spinal level) and positive airway pressure generation as a function of stimulus amplitude in representative animal. B - Mean airway pressure generation during LF-SCS (50Hz) with stimulus amplitudes of 15mA and 1mA and HF-SCS (500Hz) with a low stimulus amplitude of 1mA.

Fig. 2.

Relationships between stimulus amplitude and airway pressure generation at different stimulus frequencies during spinal cord stimulation at the T9 level. With increasing stimulus frequencies between 50 and 500Hz, there were increases in the magnitude of airway pressures. The maximum expiratory airway pressure was recorded during stimulus frequency of 500Hz.