Journal of Neuroscience Methods 268 (2016) 98–105

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Safety assessment of epidural wire electrodes for cough production in a chronic pig model of spinal cord injury

Krzysztof E. Kowalski [a,b,c], Tomasz Kowalski [a,c], Anthony F. DiMarco [a,b,*]

[a] MetroHealth Medical Center, Cleveland, OH 44106, USA
[b] Case Western Reserve University, Cleveland, OH 44106, USA
[c] Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH 44106, USA

HIGHLIGHTS

- An experimental model of chronic paraplegia was induced in mini-pigs by spinal cord compression.
- The effects of high intensity spinal cord stimulation via wire electrodes on potential tissue injury and electrode corrosion were examined.
- The application of electrical stimulation to activate the expiratory muscles results in large airway pressures characteristic of a normal cough.
- Importantly, electrical stimulation does not result in any evidence of tissue injury or electrode damage.

ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form 29 April 2016
Accepted 2 May 2016
Available online 7 May 2016

Keywords:
Expiratory muscles
Electrical stimulation
Safety
Rehabilitation

ABSTRACT

Background: It is our hypothesis that high intensity spinal cord stimulation (SCS) to restore an effective cough mechanism using wire leads, will result in significant activation of target neurons without tissue injury or electrode corrosion.
Methods: Adult mini-pigs underwent chronic spinal cord compression, followed by implantation of parallel wire leads on the dorsal epidural surface of the spinal cord, with stimulation contacts at the T9 and T12, and control electrode contacts at the T2 and T5 levels. After 3 months of daily SCS, airway pressure generation (P), tissue in the area of the stimulating and control electrodes and electrode leads were examined. P was also assessed in acute animals, which served as controls.
Results: Mean P at FRC was 54 ± 5 cmH_2O and 109 ± 11 cmH_2O in the control and chronically stimulated animals, respectively ($p < 0.05$). There was minimal tissue reaction in the area of the stimulating and control electrodes. All sets of leads revealed no evidence of electrode corrosion.
Comparison with existing methods: Previous porcine models of chronic spinal cord injury (SCI) were developed to study neurological and regenerative outcomes. Our method of chronic SCI porcine model was developed to evaluate the safety of electrical SCS to restore expiratory muscle function.
Conclusion: Chronic SCS with wire lead electrodes results in significant increases in P without evidence of significant adverse tissue reaction, nor evidence of electrode corrosion. This method may be a safe and useful technique to restore a functional cough in spinal cord injured subjects.

1. Introduction

Optimal electrical stimulation applied to implanted neural prostheses requires stimulus parameters sufficient to activate target neurons or peripheral nerves with the minimum amount of injected current. The success of the implantation also depends on the degree of tissue reaction to the electrical stimulation and any interactions between the tissue and implants. Excessive electrical stimulation can result in neural damage and/or corrosion of metallic implants.

With the goal of activating the expiratory muscles to restore cough in spinal cord injured patients, we have demonstrated in *acute* animal studies that this can be accomplished with the use of parallel wire leads positioned on the dorsal epidural surface of the spinal cord (Kowalski and DiMarco, 2011). The application of bipolar, high intensity electrical stimulation (40 V, 50 Hz, 0.2 ms pulse

* Corresponding author at: Department of Physical Medicine & Rehabilitation, Case Western Reserve University, MetroHealth Medical Center, Rammelkamp Center for Education & Research, 2500 MetroHealth Drive, R551, Cleveland, OH 44109-1998, USA. Fax: +1 216 778 8589.
E-mail addresses: kek5@case.edu (K.E. Kowalski), tomkowalski4@gmail.com (T. Kowalski), afd3@case.edu (A.F. DiMarco).

http://dx.doi.org/10.1016/j.jneumeth.2016.05.002
0165-0270/

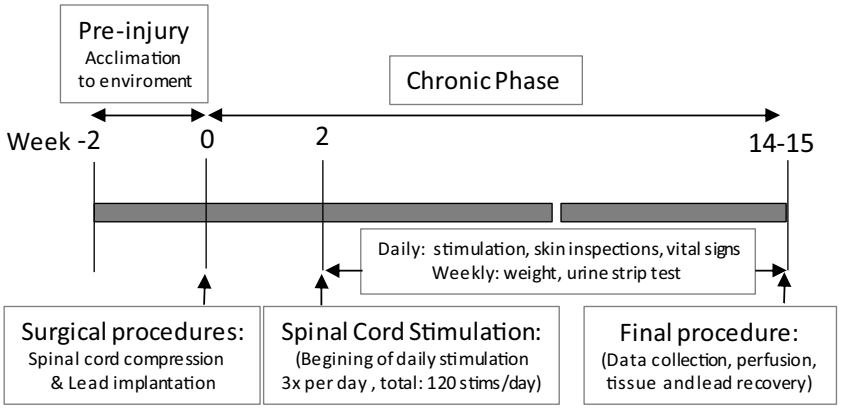

Fig. 1. Illustration of the chronic experimental procedure.

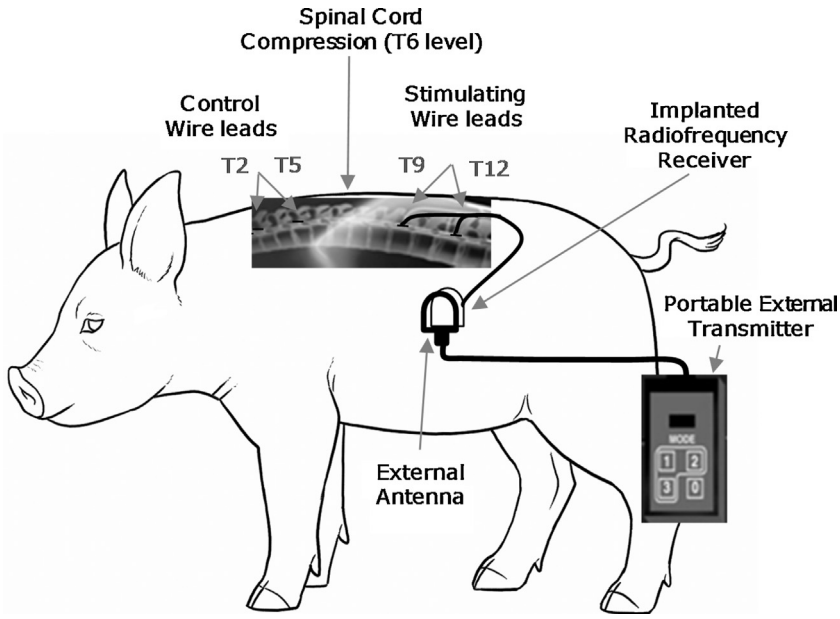

Fig. 2. Experimental setup.

width) via electrode contacts (platinum/iridium) at the T9 and T11 levels, results in large airway pressures characteristic of a normal cough.

Based upon the required stimulus parameters and a measured lead impedance of 580 Ω, the calculated charge density was ~86 μC/cm^2. This value is within the generally accepted safe limits of 100 μC/cm^2 for tissue damage and 300 μC/cm^2 for electrode corrosion (Brummer et al., 1977; Brummer and Turner, 1977; Cogan, 2008; Merrill et al., 2005; Yuen et al., 1981). Rose and Robblee (1990), however, suggested lower limits of 50–150 μC/cm^2 with 0.2 ms pulses for electrode corrosion. Moreover, only electrodes with the hemispheric geometries exhibit uniform distribution of charge density (Oldham, 2004). Many electrode designs, including wire electrodes, exhibit non-uniformity of charge density, which may result in substantially higher charge densities at the edges (Cogan, 2008; Kim et al., 1990; Wei and Grill, 2005). In addition, multiple electrodes located in close proximity were stimulated simultaneously, further increasing the potential charge density. Taken together, it is conceivable that the chronic application of these stimulus parameters is potentially harmful.

It is important to note however that most prior safety studies typically employed continuous electrical stimulation for various time periods ranging from a few hours to several weeks and with electrodes in direct contact with neural tissue. In contrast, the proposed application requires only brief intermittent stimulation (0.6 s ON-time), 120 times/day, and an extradural electrode location. Each of these factors would be expected to significantly mitigate the potential for neural injury.

The purpose of the present study therefore was to evaluate the effects of chronic electrical stimulation applied to the epidural surface of the spinal cord (T9 and T12 level) to activate expiratory muscles, in an animal model, in the same manner as that which would be employed in our planned clinical trial. Studies were performed in a chronic pig model of spinal cord injury. Outcome measures included measurements of expiratory pressure development to assess cough efficacy, tissue analysis for potential injury and electrode analysis for evidence of potential corrosion. It is our hypothesis that epidural spinal cord stimulation with wire leads, to activate the expiratory muscles, can be applied safely without the development of neural injury and/or electrode corrosion.

2. Methods

Experiments were performed on 10 mini-pigs (weight: 22.3 ± 0.8 kg) with the approval of the Institutional Animal Care and Use Committee of Case Western Reserve University. All surgi-