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Review

Activation of inspiratory muscles via spinal cord stimulation☆

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ABSTRACT

Diaphragm pacing is a clinically useful modality providing artificial ventilatory support in patients with ventilator dependent spinal cord injury. Since this technique is successful in providing full-time ventilatory support in only ~50% of patients, better methods are needed. In this paper, we review a novel method of inspiratory muscle activation involving the application of electrical stimulation applied to the ventral surface of the upper thoracic spinal cord at high stimulus frequencies (300 Hz). In an animal model, high frequency spinal cord stimulation (HF-SCS) results in synchronous activation of both the diaphragm and inspiratory intercostal muscles. Since this method results in an asynchronous pattern of EMG activity and mean peak firing frequencies similar to those observed during spontaneous breathing, HF-SCS is a more physiologic form of inspiratory muscle activation. Further, ventilation can be maintained on a long-term basis with repetitive stimulation at low stimulus amplitudes (<1 mA). These preliminary results suggest that HF-SCS holds promise as a more successful method of inspiratory muscle pacing.

1. Introduction

Cervical spinal cord injury (SCI) resulting in chronic respiratory failure is a common clinical problem. Of the 5000–6000 new cervical spinal cord injuries reported each year, nearly 20% will require mechanical ventilation (National Spinal Cord Injury Statistical Center, 2012). While most patients can eventually breathe spontaneously, approximately 5% (200–400 per year) will require chronic mechanical ventilatory support (Carter et al., 1987). These patients are subject to discomfort associated with attachment to a mechanical device, higher risk of infections, interference with speech, need for greater caregiver assistance and high costs of clinical support.

Respiratory failure occurs in patients with cervical SCI as a consequence of disruption of the bulbospinal pathways innervating the phrenic and intercostal motoneuron pools. Since the neuromuscular apparatus below the level of injury is often intact, the peripheral nerves innervating the inspiratory muscles can be electrically stimulated to restore inspiratory muscle function (Hamid and Hayek, 2008; Pancrazio and Peckham, 2009). Phrenic nerve stimulation can be applied to activate the diaphragm while upper thoracic ventral root stimulation can be applied to activate the inspiratory intercostal muscles. In fact, for the past several decades, bilateral phrenic nerve stimulation to restore diaphragm function has been a clinically accepted modality in the management of ventilator dependent tetraplegics (Adler et al., 2009; Brown et al., 2006; Carter et al., 1987; Creasey et al., 1996; DiMarco, 1999, 2001, 2004, 2009; DiMarco et al., 2002, 2005a; Dobelle et al., 1994; Elefteriades et al., 2002; Glenn et al., 1980, 1984, 1986, 1988; Glenn and Phelps, 1985; Glenn and Sairenji, 1985; Hirschfeld et al., 2008; Moxham and Shneerson, 1993; Onders et al., 2007; Peterson et al., 1994). Intercostal muscle pacing, however, remains experimental (DiMarco et al., 1987, 1989, 1994, 2005b).

While diaphragm pacing (DP) is successful in many patients in terms of eliminating or reducing the need for mechanical ventilation, current methods to provide respiratory support have the capacity to sustain full-time ventilatory support in only ~50% of patients (DiMarco et al., 1994, 2005a,b; Onders et al., 2007; Weese-Mayer et al., 1996). There is a clinical need, therefore, to develop better methods of inspiratory muscle stimulation with the capacity to generate larger inspired volumes on a repetitive basis without the development of fatigue.

In this paper, we review recent studies of a novel method of electrical activation of the inspiratory muscle activation via the application of high frequency (300 Hz) electrical stimulation on the ventral surface of the upper thoracic spinal cord. Unlike all previous methods, this technique involves activation of the inspiratory motoneuron pools resulting in more physiologic activation of the inspiratory muscles and coincident activation of both the

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diaphragm and inspiratory intercostal muscles. In theory, this technique should provide greater success in providing artificial ventilatory support to ventilator dependent tetraplegics, compared to current DP technology.

2. Brief historical perspective

Diaphragm pacing to achieve artificial ventilation has a long and rich history dating back more than 2 centuries. In the 18th century, Caldani (1786) first demonstrated in animal studies that diaphragm movement could be achieved by electrical stimulation of the phrenic nerve. Immediately following execution, Ure (1818) first demonstrated that breathing could be restored in a human by stimulation of the phrenic nerve. In the latter 19th century, Duchenne (1872) found that ventilation in humans could be restored by stimulation of moistened sponges placed over the outer borders of the sternocleidomastoid muscles. Subsequently (Sarnoff et al., 1948; Whittenberger et al., 1949), in the 1940s demonstrated that ventilation could be maintained in polio victims with percutaneous electrodes placed in the cervical region.

Major technological issues were resolved by Glenn and colleagues (Glenn et al., 1964; Van Heeckeren and Glenn, 1966) in the 1960s leading to the development and implementation of fully implantable modern-day phrenic nerve pacing systems. Other investigators have since developed systems with improved electrode design (Talonen et al., 1990; Thoma et al., 1987) and less-invasive methods of electrode placement (DiMarco et al., 2002, 2005a; Onders et al., 2004; Shaul et al., 2002). DP has been commercially available for several decades and is considered a safe and practical method of providing respiratory support in ventilator dependent patients with cervical spinal cord injury (DiMarco, 1999, 2001; DiMarco et al., 1994, 2002, 2005a; Glenn et al., 1980, 1984, 1986, 1988; Glenn and Sairenji, 1985; Onders et al., 2004; Thoma et al., 1987) and also central hypoventilation syndrome (Ali and Flageole, 2008; Brouillette et al., 1983; Hunt et al., 1988; Ilbawi et al., 1985; Tibballs, 1991; Weese-Mayer et al., 1992, 1996).

Using motor root stimulation techniques, previous studies (DiMarco et al., 1987, 1989, 1994, 2004) have also shown that the inspiratory intercostal muscles can be activated to support breathing in patients with only a single functional phrenic nerve who are, therefore, not candidates for phrenic nerve pacing.

3. Clinical relevance of diaphragm pacing

Modern day mechanical ventilators can provide reliable, portable and efficient means of respiratory support. The impact of DP, compared to mechanical ventilation, on long-term survival is unknown. Carter et al. (1987), however, compared survival rates in a retrospective analysis. Overall survival rates were similar between groups, but the patients on mechanical ventilation expired earlier than did patients maintained on DP. In a more recent clinical trial of 64 patients over a 20-year period, there was no significant difference in longevity between use of DP vs. mechanical ventilation (Hirschfeld et al., 2008). However, respiratory tract infections were a more common cause of death in the mechanical ventilation group. Additionally, there are important subjective parameters which make DP preferable to mechanical ventilation in most individuals (DiMarco, 1999, 2001, 2004, 2009; Hunt et al., 1988; Dobelle et al., 1994; Elefteriades et al., 2002; Glenn et al., 1986; Ilbawi et al., 1985; Tibballs, 1991). Perhaps since patients are using their own breathing muscles generating negative airway pressures (rather than the positive pressures generated by mechanical ventilations), they describe the sensation of more normal breathing (Brown et al., 2006; Creasey et al., 1996; DiMarco, 1999, 2001; Elefteriades and Quin, 1998; Glenn and Phelps, 1985; Glenn and Sairenji, 1985; Ilbawi et al., 1985; Moxham and Shneerson, 1993). Negative pressure ventilation may also reduce the incidence of barotrauma and have beneficial cardiovascular effects (Langou et al., 1978). Since ventilator tubing is not necessary, tension on the tracheostomy tube is eliminated, improving patient comfort. Other potential benefits include improved speech, elimination of fear of ventilator disconnection, restoration of olfactory sensation contributing to an improvement in quality of life, improvement in patient mobility, easier patient transport, elimination of ventilator noise and associated social embarrassment, and reduction in overall cost (Adler et al., 2009; DiMarco, 1999, 2001, 2004, 2009; Dobelle et al., 1994; Elefteriades et al., 2002; Fodstad, 1987, 1989). Given these advantages, most ventilator dependent SCI patients seek out DP and once they begin using these devices, have no interest in returning to mechanical ventilation.

4. Limitations of diaphragm pacing

The fact that DP is not successful in providing full-time ventilatory support in a substantial number of patients is generally due to inadequate inspired volume production (DiMarco et al., 1994, 2005a,b; Onders et al., 2007; Weese-Mayer et al., 1996). Low inspired volumes may occur for several reasons. With current methodology, electrical stimulation of the phrenic nerve is applied directly either to peripheral nerves, motor roots or functional motor points. This results in synchronous activation of all motor units within the field of stimulation and reversal of the normal recruitment order of motoneurons. Motor axons with larger diameters which innervate more fatigueable fibers are activated initially and smaller axons innervating fatigue-resistant muscle fibers are activated only at higher stimulus levels (Levy et al., 1990). Further, given their higher thresholds (Enoka, 2002; Grandjean and Mortimer, 1986; Lertmanorat and Durand, 2004; Prochazka, 1993), some axons are not activated at all resulting in incomplete diaphragm activation. With the application of chronic DP, however, the diaphragm becomes reconditioned from a muscle with a population of mixed fiber types to one with predominantly slow fibers (Acker et al., 1987; Glenn et al., 1980; Peterson et al., 1986, 1994). A benefit of this fiber type conversion is that the endurance capacity of the diaphragm is enhanced. Slow fibers, however, have relatively low maximum force-generating capacities resulting in reduced inspired volume generation.

Sub-optimal inspired volume generation during DP also occurs as a consequence of the lack of co-incident inspiratory intercostal muscle activation. While the diaphragm is clearly the primary inspiratory muscle, the intercostal muscles generate 35–40% of the inspiratory capacity (Agostoni et al., 1965). Contraction of the intercostal muscles also acts to stabilize the chest wall preventing paradoxical inward motion of the rib cage during diaphragm contraction alone.

5. High frequency spinal cord stimulation (HF-SCS) to activate the inspiratory muscles

5.1. General observations

We have recently shown in animal studies that HF-SCS results in synchronous activation of the diaphragm and intercostal muscles (DiMarco and Kowalski, 2009, 2010, 2011, 2013). All of the studies referenced in this paper related to the technique of HF-SCS have been performed in dogs anesthetized with pentobarbital sodium. Initial descriptive studies of this method indicated that both the diaphragm and inspiratory intercostal muscles can be activated in concert with the application of electrical stimulation on the epidural surface of the upper thoracic spinal cord at high stimulus