Neural prostheses in the respiratory system

Anthony F. DiMarco, MD
Rammelkamp Research Center and MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH

Abstract—Approximately 5% of spinal cord-injured individuals suffer from respiratory muscle paralysis and require chronic mechanical ventilation. Unfortunately, this form of life support is associated with a number of undesirable side effects and discomforts. The only available alternative to mechanical ventilation is diaphragm pacing via bilateral phrenic nerve stimulation. This technique can provide patients with marked improvements in life quality and offers significant advantages compared to mechanical ventilation. Many patients, however, do not have bilateral phrenic function or are not willing to accept the risks inherent with phrenic nerve pacing and therefore are not candidates for this technique. Two alternative methods to ventilate patients with ventilator-dependent tetraplegia are reviewed in this paper. In patients with only a single functional phrenic nerve who are therefore not candidates for phrenic nerve pacing, combined intercostal muscle and unilateral phrenic nerve stimulation has recently been shown to maintain ventilatory support. In patients with bilateral phrenic nerve function, on-going studies suggest that intra-muscular diaphragm pacing may be a useful alternative to direct phrenic nerve pacing. With the electrodes placed into the diaphragm laparoscopically, this method allows for the diaphragm to be activated without manipulation of the phrenic nerve, need for thoracotomy, or hospitalization. Both techniques provide benefits similar to that derived from bilateral phrenic nerve pacing and hold promise as alternative methods of ventilatory support in selected populations groups.

Key words: diaphragm pacing, FES, intercostal muscle pacing, phrenic nerve stimulation, respiratory paralysis.

INTRODUCTION

There are an estimated 183,000 to 230,000 individuals with spinal cord injury (SCI) in the United States (1). On average, 11,000 new injuries are reported every year (1); nearly 52 percent of SCI are sustained at the cervical level (1). Because of the high incidence of respiratory compromise associated with these injuries, approximately 20 percent of patients will require mechanical ventilatory support. Unfortunately, many patients cannot be weaned off mechanical ventilation, and consequently, approximately 5 percent (200–400 per year) will require chronic mechanical ventilation (2).

There are a number of undesirable side effects associated with mechanical ventilation, including risk of infection, interference with speech, increased need for assistance, and high costs. The only available alternative
therapy is bilateral phrenic nerve stimulation to pace the diaphragm, a technique that has been in clinical use for the past two decades (3–8). Compared to mechanical ventilation, diaphragm pacing provides patients with increased mobility, improved speech, reduced level of nursing care, and possibly reduced volume of respiratory secretions and incidence of respiratory tract infections (7,9–14). Other benefits include an improved sense of well being and overall health, reduced anxiety and elimination of fear of ventilator disconnection, reduced embarrassment and stigma caused by ventilator tubing and noise, and an overall reduction in costs (14–16).

Most patients with cervical SCI and dependence on mechanical ventilation, however, are not candidates for this technology. First, many patients do not have intact bilateral phrenic nerve function. Second, many patients with normal phrenic nerve function are reluctant to assume the risks associated with phrenic nerve pacing, which include possible damage to the phrenic nerves as well as the surgical risks, hospitalization, and high cost associated with the requisite thoracotomy.

This paper will review our experience with two possible alternatives to phrenic nerve stimulation that may be useful in selected patient groups. In patients with only a single functional phrenic nerve, combined intercostal and unilateral phrenic nerve pacing can also provide long-term ventilatory support (17–19). The second technique, intramuscular diaphragm pacing, is a method by which electrodes are placed directly into the diaphragm itself via laparoscopic surgery (20) rather than on the phrenic nerves. Consequently, direct manipulation and possible injury to the phrenic nerves are avoided. Moreover, the need for a thoracotomy is averted.

Respiratory Anatomy

Respiratory rhythm is generated in the respiratory center located in the lower medulla. Impulses from this center pass along the spinal cord and synapse with motor neurons in the cervical region of the spinal cord to innervate the sternocleidomastoid and scalenus muscles (accessory muscles of inspiration) and diaphragm (the major inspiratory muscle). Neurons from the C3, C4, and C5 spinal cord levels form the phrenic nerves, which innervate the diaphragm. Impulses from the respiratory center also synapse with the intercostal motor neurons, which innervate the inspiratory and expiratory intercostal muscles and abdominal muscles.

There are two portions of the diaphragm: the costal portion, which originates from the lower ribs, and the crural portion, which originates from the vertebral column; both portions insert on the central tendon (Figure 1). The other principal inspiratory muscle group is the intercostal muscles, which are positioned between the ribs. These include (a) the parasternal intercostal muscles, so called because of their location adjacent to the sternum, (b) the external intercostal muscles, located more laterally, and (c) the levator costi muscles, located posteriorly. The main muscles of expiration are the internal intercostal and abdominal muscles.

Intercostal Muscle Stimulation

Animal experiments

While the diaphragm is the primary respiratory muscle, the inspiratory intercostal muscles are also an important respiratory muscle group, generating approximately 35 to 40 percent of the inspiratory capacity (23). A reproducible method to activate these muscles would be a useful technique to restore inspiratory muscle function in ventilator-dependent tetraplegic patients who do not have normal phrenic nerve function. Electrical activation of the intercostal muscles to achieve inspired volume, however, is much more difficult than activation of the diaphragm as there are 12 pairs of intercostal muscles on each side of the thorax, compared to only two phrenic nerves. In preliminary animal studies conducted in a dog model, an attempt was made to place electrodes within six, eight, and ten intercostal muscles or nerves to generate inspired volume. While somewhat effective in generating volume, this method proved to be both tedious and technically very
DiMARCO: Neural prostheses for ventilation
difficult. Consequently, alternative approaches were investigated to activate this muscle group.

In animal experiments, the application of electrical current with a disc electrode positioned on the dorsal surface of the spinal cord was found to generate large inspired volumes (17). By trial and error, stimulation in the vicinity of the T2 region was found to result in maximum inspired volume production (22). Since the phrenic nerves were cut in these animals, the generated inspired volumes were consequent to intercostal muscle activation alone. Stimulation of the intercostal muscles by this technique resulted in inspired volumes that were approximately 75 percent of the magnitude of volumes generated with bilateral diaphragm stimulation (Figure 2). Since stimulation was applied nonspecifically to the upper thoracic nerves, however, this technique resulted in contraction of some nonrespiratory muscles, as well. Consequently, contraction of the upper chest wall and upper extremity muscles was also observed in these experiments.

We also evaluated the efficacy of long-term intercostal activation via spinal cord stimulation (SCS) to maintain artificial ventilation (23). In dog experiments, the phrenic nerves were severed bilaterally to eliminate diaphragm action. SCS was provided 13 to 14 times per minute, with an inspiratory time of 1.2 seconds and a total respiratory cycle time of 4.6 seconds to simulate artificial respiration. Stimulation was provided for up to 6 hours in each animal. The pressure-time index, a measure of intercostal muscle work, was calculated as the product of inspiratory time divided by total cycle time multiplied by the airway pressure during pacing divided by maximal airway pressure generation. The pressure-time index achieved in this experiment was 0.12, a value that indicates that the intercostal muscles should not develop fatigue with chronic stimulation, based upon studies performed on the diaphragm (1). A recording of the intercostal emg pattern and tidal volume generation is shown in Figure 3.

During chronic stimulation studies with intercostal muscle pacing alone to maintain ventilation, inspired volume production, and arterial oxygen (PaO₂) and carbon dioxide gas tensions (PaCO₂) remained stable over a 6-hour period. In fact, over the time course of these experiments, both PCO₂ and PO₂ levels remained in the normal range. Similar results were obtained in a few animals in which the experiment was extended to 10 to 12 hours. We concluded from this study that the intercostal muscles could be activated via SCS to provide adequate ventilation for prolonged time periods without evidence of fatigue.

Clinical trials
The technique of intercostal muscle pacing has been applied to ventilator-dependent tetraplegic patients with phrenic nerve injury in attempt to provide ventilatory support (Figure 4). In the first clinical trial of this technique, the patient population consisted of five males with ventilator-dependent tetraplegia (19). The time since injury ranged from 9 months to more than 7 years. The spontaneous vital capacity in these individuals ranged between 50 ml and 250 ml (normal subjects have a vital capacity in the range of 5–6 liters). In each subject, four electrode disks were placed on the ventral epidural surface of the spinal cord at the T2 level through a hemilaminectomy. One of the subjects had to be excluded from the study because of cystic degeneration of the spinal cord.

![Figure 2.](image_url)

**Figure 2.**
Inspired volume generation during intercostal stimulation alone, diaphragm stimulation alone, and combined intercostal and diaphragm stimulation in an animal model. Volumes generated during combined stimulation were equal to those generated by sum of intercostal and diaphragm stimulation alone.

![Figure 3.](image_url)

**Figure 3.**
Recording of airway pressure, parasternal emg, and tidal volume during spinal cord stimulation in an animal model.
The inspiratory muscles are atrophied (23) in patients who have been ventilator-dependent for prolonged time periods. Consequently, the initial inspired volumes in these patients were quite small and reconditioning over a period of several weeks was necessary to reverse the effects of atrophy. Over the 24-week period of the clinical trial of gradually increasing the hours per day of intercostal muscle stimulation, there was a gradual increase in inspired volume production. Following reconditioning in these patients, maximum tidal volumes during chronic stimulation ranged between 300 and 500 ml, vital capacities between 470 to 850 ml, and negative inspiratory pressures from 8.5 to 19.5 cm of water (the minimum pressure required to maintain adequate ventilation is usually between 18 and 20 cm). However, unlike the animal studies in which long-term ventilatory support was achieved, the maximum time these patients could be maintained off mechanical ventilation ranged from 15 minutes to approximately 3 hours (19).

In terms of side effects, there was considerable movement of the upper torso and arms with maximum stimulation. However, when the stimulus current was ramped down to those levels resulting in the chronic pacing parameters, there was only minimal visible contraction of nonrespiratory muscles. By the end of the reconditioning period, there was visible development of each subject’s upper body musculature.

Although intercostal muscle pacing alone was not successful in maintaining substantial time off mechanical ventilation, we surmised that this technique might be useful in patients with only one functional phrenic nerve who are therefore not candidates for phrenic nerve pacing. In this patient population, combined intercostal and unilateral phrenic nerve pacing should provide adequate inspired volume generation to maintain long-term ventilation.

In our second clinical trial, four ventilator-dependent tetraplegic patients with only a single intact phrenic nerve were enrolled (17). This group included three males and one female with SCI between the levels of C2 and C4. The time since injury ranged between 2 and 12 years. Their spontaneous vital capacities ranged between 50 and 650 ml, and none of these patients could breathe on their own for more than 15 to 20 minutes. As in our initial clinical trial, electrodes were placed on the ventral epidural surface of the spinal cord at the T2 level via a cervical hemilaminectomy to activate intercostal muscles; a conventional phrenic nerve electrode was placed via thoracotomy to activate the diaphragm.

Initially, very small volumes resulted from electrical stimulation of the diaphragm and intercostal muscles. As the diaphragm and intercostal muscles were progressively reconditioned over several weeks, however, inspiratory volumes reached approximately 600 ml when either muscle group was stimulated independently. During combined intercostal muscle and phrenic nerve stimulation, inspiratory volumes ranged between 750 and 1,300 ml following reconditioning in three of the four subjects. These volumes are in the range of that usually seen with bilateral phrenic nerve pacing. The fourth patient was a woman of small stature (4’10”) and as a result, her

Figure 4. Hardware employed during combined intercostal and diaphragm pacing.
volumes were significantly smaller. Yet she also demonstrated incremental increases in inspiratory volume production as the reconditioning program progressed (Figure 5). With combined stimulation, this patient also produced inspired volumes that were approximately equal to the sum of the volumes achieved by either muscle group alone. In the four subjects, maximum negative inspiratory pressures ranged from 20 to 80 cm H₂O.

When we applied combined intercostal and diaphragm pacing with chronic pacing parameters in these four subjects, tidal volumes ranged between 350 ml (for the smallest subject) to 850 ml. Importantly, these patients were able to achieve substantial time off mechanical ventilatory support. While most patients were able to maintain full time support, each elected to be maintained on mechanical ventilation at night. When asked to rate the level of breathing comfort with this pacing technique on a scale of zero to ten, zero being mechanical ventilation and ten being normal breathing, all four patients reported a level of comfort very near normal breathing.

It is also important to note that time since injury did not impact the potential for intercostal stimulation to generate large inspired volumes. Thus, patients who have been ventilator-dependent for many years may still benefit from this procedure.

**Intramuscular Diaphragm Pacing**

**Animal experiments**

As discussed earlier, conventional phrenic nerve pacing has significant disadvantages that make it an unacceptable option for many ventilator-dependent tetraplegic patients. First, this procedure carries the risk of phrenic nerve injury. Since many patients have hope of complete restoration of function, they are not willing to undergo any procedure with the potential to cause further neurologic injury. Secondly, phrenic nerve pacing requires a thoracotomy, which has associated surgical risks and need for hospitalization. Though the surgical risk may be negligible in a noncompromised patient, it may be significantly higher in tetraplegic patients with a chronic tracheostomy on mechanical ventilation who may be prone to respiratory tract infections. Finally, phrenic nerve pacing is quite expensive. In addition to the cost of the surgical procedure, the 5- to 10-day hospitalization cost is in the range of $80,000 to $100,000. There are also additional costs for equipment, supplies, and personnel (2).

To obviate some of these disadvantages, we have begun a clinical trial of intramuscular diaphragm pacing, a technique by which electrodes implanted directly into the diaphragm activate the phrenic nerves (20). The advantages of this method are that phrenic nerve dissection is not required and therefore the risks of phrenic nerve injury are virtually eliminated. Moreover, a thoracotomy is not needed since the electrodes are implanted into the diaphragm via laparoscopic surgery.

The sentinel work suggesting that intramuscular electrodes could be used to pace the diaphragm was the demonstration in animal studies that stimulation applied with electrodes positioned in the vicinity of the phrenic nerve motor points resulted in large inspired volumes (25,26). This data demonstrated a virtually linear relationship between tidal volumes resulting from direct phrenic nerve stimulation and intramuscular diaphragm stimulation.

Translating this work to human patients, however presented many challenges. First a noninvasive method of obtaining access to the abdominal surface of the diaphragm had to be developed. Second, an electrode had to be designed that could last for significant periods of time without damage and without causing injury to the diaphragm. Finally, a technique had to be developed to safely place an electrode directly into the relatively thin diaphragm (2–4 mm thick in humans) (27–29).

**Clinical experience**

To date, one patient has been enrolled in this clinical trial (20). He is a 35-year-old male with a C₂ level SCI secondary to a diving accident. He had normal bilateral phrenic nerve function. Intramuscular diaphragm
electrodes were implanted via laparoscopic surgery in March 2000 (Figure 6).

For the motor points of the diaphragm to be located, the change in abdominal cavity pressure was mapped against the applied stimulus amplitude for different stimulus sites on the diaphragmatic surface. A test suction electrode, which could be applied and removed without causing diaphragm injury, was used to locate the motor points. The motor points were identified as those sites resulting in maximum output in terms of pressure generation with the lowest stimulus currents. With the overlapping of the response curves obtained from the stimulation of multiple sites (aided by computer analysis), the specific motor points on each hemidiaphragm were identified. Permanent intramuscular electrodes were implanted at these sites.

The diaphragm was initially activated for 10 to 15 minutes per hour for 6 to 8 hours per day. The duration of stimulation was gradually increased over the course of the reconditioning program. Initial inspiratory volumes were approximately 400 ml; over the course of the 20-week reconditioning period, inspired volumes gradually increased to 1.1 liters. The maximum inspiratory volumes achieved were in the range of that achieved with bilateral phrenic nerve pacing. The hours of pacing per day (12–14 breaths/min) were gradually increased to 24 hours after 20 to 25 weeks of daily stimulation. This subject has been off mechanical ventilatory support for the past 5 months. If similar results are obtained in additional patients, this technique has the potential to replace conventional phrenic nerve pacing techniques.

**CONCLUSION**

In selected patients with ventilator-dependent tetraplegia, there are new emerging options for respiratory muscle pacing. In patients with only a single functional phrenic nerve, combined intercostal and unilateral diaphragm pacing can maintain near full-time ventilatory support. In patients with bilateral phrenic nerve function, intramuscular diaphragm pacing offers significant advantages compared to conventional phrenic nerve pacing. By this technique, electrodes are placed directly into the diaphragm muscle via laparoscopic surgery. Since the electrodes are not placed in direct contact with the phrenic nerve and phrenic nerve dissection is not required, the risk of phrenic nerve injury is virtually eliminated. Moreover, since laparoscopic surgery is generally performed in the outpatient setting, the morbidity, need for hospitalization, and associated high costs of a thoracotomy are eliminated. Ventilation by these alternative means also appears to provide both health and lifestyle advantages to the user similar to that achieved with conventional phrenic nerve pacing.

**ACKNOWLEDGMENTS**

This paper arose from a presentation at the Case Western Reserve University “Applied Neural Research Day” on June 16, 2001, in Cleveland, Ohio.

**REFERENCES**
