Phrenic Nerve Pacing Via Intramuscular Diaphragm Electrodes in Tetraplegic Subjects*

Anthony F. DiMarco, MD, FCCP; Raymond P. Onders, MD; Anthony Ignagni; Krzysztof E. Kowalski, PhD; and J. Thomas Mortimer, PhD

Context: Diaphragm pacing in ventilator-dependent tetraplegic subjects is usually achieved by the placement of phrenic nerve electrodes via thoracotomy. However, this technique may be accomplished less invasively via laparoscopic placement of IM electrodes, at a lower cost and with less risk of injury to the phrenic nerve. 

Objective: To assess the feasibility of laparoscopic placement of IM diaphragm electrodes to achieve long-term ventilatory support in ventilator-dependent tetraplegic subjects.

Design, setting, and participants: Two IM diaphragm electrodes were placed laparoscopically in each hemidiaphragm in five subjects with ventilator-dependent tetraplegia. Studies were performed either on an outpatient basis or with a single overnight hospitalization. Ventilator-dependent tetraplegic subjects were identified in whom bilateral phrenic nerve function was present, as determined by phrenic nerve conduction studies. Following electrode placement, subjects participated in a conditioning program to improve the strength and endurance of the diaphragm over a period of 15 to 25 weeks. The duration of the study was variable depending on the time necessary to determine the maximum duration that individuals could be maintained without mechanical ventilation support.

Main outcome measures: Magnitude of inspired volume generation and duration of ventilatory support with bilateral diaphragm pacing alone.

Results: In four of the five subjects studied, initial bilateral diaphragm stimulation resulted in inspired volumes between 430 and 1,060 mL. Reconditioning of the diaphragm over several weeks resulted in substantial increases in inspired volumes to 1,100 to 1,240 mL. These subjects were comfortably maintained without mechanical ventilatory support for prolonged time periods by diaphragm pacing, by full-time ventilatory support in three subjects, and 20 h per day, in the fourth subject. No response to stimulation was observed in one subject, most likely secondary to denervation atrophy.

Conclusions: Diaphragm pacing in ventilator-dependent tetraplegic subjects can be successfully achieved via laparoscopic placement of IM electrodes.

Key words: diaphragm pacing; laparoscopy; spinal cord injury

Abbreviation: PNP = phrenic nerve pacing

Over the past several decades, a variety of methods have been suggested to activate the phrenic nerves to achieve artificial ventilation.1–5 The most practical and successful technique of phrenic stimulation, however, was developed by Glenn and colleagues,1,6 a method that has remained the “gold standard” of clinical application for > 20 years. This technique, applied predominantly in subjects with ventilator-dependent tetraplegia, has provided several clinical advantages compared to mechanical ventilation.7 While the technique of phrenic nerve pacing (PNP) has undergone some refinements, predominantly in the method of application of electrical stimuli to the nerve,3,4 this method usually requires a thoracotomy, with its associated risks and high cost. In addition, this technique carries some risk of phrenic nerve injury since manipulation of the phrenic nerves is required for electrode placement.8,9 Damage to the phrenic nerves could result in inadequate inspired volume generation and the consequent development of respiratory failure.

In this report, we describe a new method by which the phrenic nerves can be activated to provide long-term ventilatory support (ie, through laparoscopic placement of IM diaphragm electrodes). This technique has the potential to provide a less invasive and more convenient method of phrenic nerve stimulation with a lower cost in ventilator-dependent tetraplegic subjects.

Materials and Methods

Subjects

Five subjects with trauma-induced high cervical spinal cord injury who required long-term mechanical ventilatory support were studied. All subjects were in stable condition at the time of treatment from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

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study (ie, free of significant lung, cardiovascular, or brain disease). Highly motivated subjects with sufficient caregiver support were recruited for this study. This investigation was approved by the US Food and Drug Administration (Investigational Device Exemption G920162) and also by the institutional review boards of the MetroHealth Medical Center and University Hospitals. Informed consent was obtained from each subject prior to enrollment in the study.

The clinical data of the subjects who participated in this study are shown in Table 1. All subjects were male, had experienced traumatic injury to the upper cervical spinal cord, and had required full-time ventilatory support since the time of injury. The elapsed time since injury ranged from 1 to 8 years. At the time of recruitment into the study, the spontaneous vital capacities ranged between 280 and 890 mL. Each of the subjects was hyperventilated while receiving mechanical ventilation. In each case, ventilator adjustments were attempted to restore PaCO₂ to more normal values per subject tolerance. The ventilator settings and arterial blood gas measurements of each of the subjects are shown in Table 2. Each of the subjects recruited for this study could tolerate at least 20 min without mechanical ventilation, but none could comfortably tolerate spontaneous breathing for > 1 to 2 h. Chest radiograph findings were normal in two subjects but could tolerate at least 20 min without mechanical ventilation, but none could comfortably tolerate spontaneous breathing for > 1 to 2 h. Chest radiograph findings were normal in two subjects but demonstrated basilar atelectasis in the others. Each subject had normal bilateral phrenic nerve function, as determined by phrenic nerve conduction studies.

**Electrode Placement**

The abdominal surface of the diaphragm was visualized for electrode placement utilizing standard laparoscopic techniques. Since uniform diaphragm activation required the placement of IM electrodes near the entrance points of the phrenic nerves into each hemidiaphragm10–13 (phrenic nerve motor points shown in Fig 1) and the phrenic nerves are not visible on the abdominal surface of the diaphragm, methods were devised to determine the location of the motor points. A previously described mapping procedure14–17 was performed for this purpose. This technique first entailed the evaluation of several test sites in the general region of the motor points (based on previous anatomic studies) with a suction electrode, which could be reversibly applied to the region of the motor points (based on previous anatomic studies) first entailed the evaluation of several test sites in the general region of the motor points (based on previous anatomic studies) with a suction electrode, which could be reversibly applied to the region of the motor points (based on previous anatomic studies). In our initial subject, a current distance model was used to more precisely determine the location of the motor points (ie, the coarse mapping procedure). In our initial subject, a current distance model was used to more precisely determine the location of the motor points (ie, the coarse mapping procedure). This procedure was time-consuming, and required measurements of intraabdominal pressure (Valkyne Engineering Corp; Northridge, CA) over a broad range of stimulus currents and the determination of the minimum current value for full diaphragm recruitment at several sites. Mathematical analyses of these data from several sites were used to predict the approximate location of the motor points for subsequent permanent electrode placement. This technique was successfully used in the evaluation of the left hemidiaphragm but was unsuccessful on the right hemidiaphragm because we failed to notice that the phrenic nerve entered on the central diaphragm with an anterior branch that was outside of the mapping field. In this subject, a second surgical procedure was required in which two electrodes were placed in the right hemidiaphragm, one that resulted in the contraction of the anterior portion and a second that resulted in the contraction of the posterior portion of the diaphragm, as determined by visual observation.

In subsequent subjects, we made more systematic use of the coarse mapping procedure. We found that the potential implant sites could be readily identified by visual observation of the portion of the diaphragm that had been activated and by the magnitude of the abdominal pressure change. From these observations and from our experience that the fine mapping technique was time-consuming, it was deemed that the target implant sites could be adequately determined by the visual assessment of sites, which resulted in uniform diaphragm contraction and large changes in intraabdominal pressure, both by twitch stimulation and high-frequency stimulation. This latter method also had the advantage of much more rapid evaluation and was therefore utilized in each of the subsequent subjects.

Using the coarse mapping technique, an initial permanent electrode18 was placed using a unique tool to implant the IM electrodes19 in each hemidiaphragm. This was followed by the placement of a second electrode in a location that also provided the recruitment of a major portion of the muscle, usually within 1 to 2 cm of the initial electrode location. Repeat visual assessment and determination of intraabdominal pressure was made following each electrode insertion. Wires from the electrodes were brought out through the epigastric port and tunneled subcutaneously to the right or left subclavicular region where they exited the chest wall, as described previously.

The monitoring of cardiac rhythm during maximum diaphragm stimulation was observed in the operating room in each subject. No arrhythmias were observed during electrical stimulation.

**Muscle Reconditioning**

Approximately 2 weeks following the placement of the diaphragm electrodes, inspired volume generation was evaluated with each of the four electrodes individually. Relationships between stimulus amplitude (pulse width, 0.1 ms) and inspired volume at constant stimulus frequency, and between stimulus frequency and inspired volume at constant stimulus amplitude also were determined. In each instance, the maximum or near-maximum amplitude was required to achieve the maximum inspired volume generation. Consequently, 24 or 25 mA (depending on the stimulator employed) was applied at each instance during long-term stimulation. Subsequently, the interaction between the two electrodes implanted in each hemidiaphragm was assessed. During the early portion of the reconditioning period, the stimulation of both electrodes within each hemidiaphragm generally resulted in greater inspired volumes.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Weight, lb</th>
<th>Cause of Injury</th>
<th>Level of Injury</th>
<th>Elapsed Time Since Injury</th>
<th>Spontaneous Vital Capacity, mL</th>
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</thead>
<tbody>
<tr>
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<td>Male</td>
<td>220</td>
<td>Diving accident</td>
<td>C2</td>
<td>1 yr 8 mo</td>
<td>890</td>
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<tr>
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<td>Male</td>
<td>225</td>
<td>Horseback riding accident</td>
<td>C2</td>
<td>8 yr</td>
<td>550</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>220</td>
<td>Motor vehicle accident</td>
<td>C3–C4</td>
<td>2 yr</td>
<td>480</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>181</td>
<td>Motorcycle accident</td>
<td>C3</td>
<td>1 yr</td>
<td>500</td>
</tr>
<tr>
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<td>Male</td>
<td>208</td>
<td>Bicycle accident</td>
<td>C2</td>
<td>5 yr</td>
<td>280</td>
</tr>
</tbody>
</table>

*All patients experienced traumatic cervical spinal cord injury, and the level of injury was based on motor and sensory deficits.

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**Table 1—Clinical Data for the Tetraplegic Subjects**
compared to the stimulation of one electrode alone. In some instances, increases in pulse width to 0.150 ms resulted in greater inspired volumes, and this higher pulse width was employed. Pulse widths above this value were not applied during long-term stimulation due to safety concerns related to electrode corrosion. In each subject, the initial applied stimulus frequency was 20 Hz. During the conditioning period, attempts were made to gradually reduce the stimulus frequency to the lowest value that resulted in adequate ventilation. Inspiratory time (ie, train duration) was set at 1.1 s, and the respiratory rate was set between 10 and 12 breaths/min.

Initially, pacing was provided for 5 to 10 min each hour for 5 to 6 h per day and was gradually increased, as tolerated. When continuous pacing for 6 to 8 h was achieved, the number of hours per day of pacing was increased over time.

During muscle reconditioning, a multifunction monitor (model N-100; Nellcor; Hayward, CA) was used to monitor arterial oxygenation and end-tidal PCO₂ via a finger probe at the tracheal opening. Arterial blood gases were sampled intermittently.

Tidal volume was monitored by the electrical integration of the flow signal at the tracheal opening using a pneumotachograph (model 3700; Hans Rudolph; Kansas City, MO) and also with a respirometer (Wright respirometer, model Mark 14; Ferraris Medical Ltd; Enfield, UK). Airway pressure was monitored intermittently during airway occlusion for a single breath using a differential pressure transducer (Validyne MP; Validyne). Measurements were recorded on an eight-channel strip chart recorder (model DASH8; Astro-Med; Warwick, RI).

In subject 3, no appreciable inspired volume could be achieved with diaphragm stimulation. This represented either a false-positive phrenic nerve conduction study or phrenic nerves that were inaccessible to IM diaphragm stimulation. Under direct observation, the appearance of the diaphragm in this subject appeared quite thin compared to the other subjects, suggesting denervation atrophy. The following results therefore represent data on the remaining four subjects.

With the exception of one subject in which electrodes were positioned several centimeters apart in the right hemidiaphragm, both IM diaphragm electrodes in each hemidiaphragm were placed within 1 to 2 cm of each other. Moreover, the stimulation of each of these electrodes appeared to result in the contraction of both the anterior and posterior portions of the hemidiaphragm. Following reconditioning in three subjects, the stimulation of two electrodes resulted in greater inspired volumes than either one alone, and therefore artificial ventilation was maintained with the stimulation of all four electrodes. In one subject, the stimulation of one electrode within each hemidiaphragm provided inspired volumes that were similar to that achieved with both electrodes, and, therefore, artificial ventilation was provided with one electrode in each hemidiaphragm.

**RESULTS**

Maximum changes in inspired volume resulting from separate left and right hemidiaphragm stimulation and bilateral stimulation, at various intervals during the reconditioning period, are superimposed for one subject in Figure 2. There were progressive increases in inspired volume generation during unilateral and bilateral diaphragm stimulation. Since the inspiratory time was constant at 1.1 s under all conditions, increases in inspired volume were achieved by increases in inspiratory flow rate. This subject achieved maximum inspired volumes of 450, 420, and 1,100 mL during right, left, and bilateral stimulation, respectively. Similar results were observed in the other subjects.

The changes in inspired volume resulting from separate left, right, and bilateral diaphragm stimulation over the course of the reconditioning period is shown in Figure 3 for each of the four subjects who completed the program. During unilateral maximum stimulation, the inspired volume ranged between 180 and 470 mL, and gradually increased to between 400 and 560 mL. Initial inspired volumes resulting from bilateral diaphragm stimulation ranged between 430 and 1,060 mL, and gradually increased to between 1,100 and 1,240 mL. The increases in inspired volume resulting from unilateral diaphragm stimulation were variable. The smallest changes resulting from bilateral stimulation were observed in subject 4, whose injury had occurred most recently, 12 months previously.

The changes in esophageal, gastric, and airway pressures during long-term bilateral stimulation (11 Hz) and

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### Table 2—Ventilatory Characteristics in Tetraplegic Subjects*

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>pH</th>
<th>PCO₂, mmHg</th>
<th>PO₂, mmHg</th>
<th>O₂ Saturation, %</th>
<th>VT, mL</th>
<th>RR, breaths/min</th>
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</thead>
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<td>7.39</td>
<td>34</td>
<td>120</td>
<td>98</td>
<td>1,250</td>
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<td>96</td>
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<td>7.52</td>
<td>24</td>
<td>86</td>
<td>99</td>
<td>1,100</td>
<td>12</td>
</tr>
</tbody>
</table>

*VT = tidal volume; RR = respiratory rate.

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*Ventilator Settings*

Ventilatory Characteristics in Tetraplegic Subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>pH</th>
<th>PCO₂, mmHg</th>
<th>PO₂, mmHg</th>
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<th>RR, breaths/min</th>
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<td>24</td>
<td>86</td>
<td>99</td>
<td>1,100</td>
<td>12</td>
</tr>
</tbody>
</table>

*VT = tidal volume; RR = respiratory rate.
maximum stimulation (50 Hz) following reconditioning were measured in one subject. Maximum airway and transdiaphragmatic pressures in this subject were 65 and 96 cm H₂O, respectively. Diaphragm contraction was associated with an obvious expansion of the abdominal wall and lower rib cage, and an inward recoil of the upper rib cage.

The relationship between stimulus frequency and inspired volume generation is shown for one subject in Figure 4. During the initial stimulation, there were progressive increases in inspired volume generation with increasing stimulus frequency under each condition. Over the course of the reconditioning period, there were progressive increases in inspired volume generation under each condition at each stimulation frequency, such that each curve became shifted upward and to the left. Similar responses were observed in the other subjects.

The inspired volumes achieved during long-term pacing and the maximum tolerated pacing duration are shown for each subject in Table 3. Long-term pacing volumes were selected for patient comfort and to allow subjects to speak normally. Each of the subjects achieved substantial independence from mechanical ventilatory support (ie, full-time ventilatory support in three subjects, and 20 h per day in the remaining subject). All four subjects indicated that diaphragm pacing provided substantial subjective improvement in breathing comfort level compared to that with mechanical ventilation. End-tidal Pco₂ values during long-term pacing ranged between 30 and 32 mm Hg.

The interaction between left and right unilateral diaphragm stimulation was examined by comparing the arithmetic sum of inspired volumes achieved by unilateral stimulation and the inspired volumes achieved during bilateral stimulation. The maximum inspired volumes generated during unilateral and bilateral diaphragm stimulation are shown for each subject in Table 4. In each instance, the arithmetic sum of inspired volumes during right and left diaphragm stimulation alone was lower than the volumes achieved with bilateral diaphragm stimulation, indicating a synergistic effect of bilateral stimulation.

**DISCUSSION**

In a previous case report, we described the first tetraplegic subject in whom full-time diaphragm pacing could be maintained via IM diaphragm electrodes. In the current report, additional clinical experience with this technique and a modification of the method of electrode insertion has been presented. The results indicate that artificial ventilation via IM diaphragm pacing provides a similar degree of ventilatory support and clinical benefit to ventilator-dependent tetraplegic subjects when compared to conventional PNP. By this new technique, however, stimulating electrodes can be placed less invasively on an outpatient basis or a single-night hospital stay, resulting in less risk, a substantial cost saving, and greater convenience.

**Comparison With Conventional Diaphragm Pacing**

Based on previously published reports, the magnitude of inspired volumes generated by phrenic nerve stimulation via IM electrodes is comparable to that achieved with conventional PNP. The maximum airway and transdiaphragmatic pressures measured in one subject were also similar to values previously reported for conventional PNP. Importantly, end-tidal Pco₂ measurements were maintained in the low normal range with long-term pacing parameters in each of the subjects. Taken together, these data indicate that the activation of the diaphragm by IM electrodes results in a comparable level of diaphragm activation when compared to direct phrenic nerve stimulation.

The subjects in the present study also reported clinical benefits of diaphragm pacing that were similar to those described with conventional PNP, including improved sense of smell, more comfortable breathing, improved speech, greater independence, and elimination of the fear of disconnection from the mechanical ventilator.

Conventional PNP generally requires a thoracotomy, which is a major surgical procedure with associated risks, a required in-patient hospital stay, and high cost. In addition, the manipulation of the phrenic nerves, a proce-
dure that carries some risk of nerve injury, is required. These disadvantages have limited the number of patients undergoing this procedure and present a significant obstacle to those patients undergoing this procedure. Laparoscopy, in contrast, is a less invasive procedure with obvious cosmetic benefits and is often performed on an outpatient basis. Due to the investigational nature of the laparoscopic placement of diaphragm electrodes, most subjects in the present study were admitted to the hospital overnight for observation. With greater clinical experience, however, it is likely that this procedure also can be performed on an outpatient basis, as was done following the second surgical procedure in the initial subject.

Some studies have demonstrated that phrenic nerve electrodes can also be placed thoracoscopically in children for management of congenital central hypoventilation syndrome. While obviating the need for a thoracotomy, this technique still requires the manipulation of the phrenic nerves and is technically quite challenging. It is also not clear whether this procedure can be performed successfully in adults. Since laparoscopic IM electrode placement, as described in the present study, does not involve direct contact with the phrenic nerve, the risk of nerve injury is virtually eliminated.

Diaphragm Mapping and Determination of Electrode Insertion Sites

Uniform diaphragm activation requires the placement of IM electrodes near the phrenic nerve motor points (i.e., the area of the muscle contained within the space defined by the entrance points of the phrenic nerves into the diaphragm). An important finding of the present study was that the coarse mapping procedure, performed with a suction electrode in the general vicinity of the motor point (based on previous anatomic evaluations), and the visualization of the contraction of both anterior and posterior portions of the diaphragm were deemed sufficient to determine the optimal sites for permanent electrode placement. Stimulation in these same regions also resulted in the largest increases in intraabdominal pressure. Therefore, performance of the previously described fine mapping technique involving a complex mathematical analysis was discontinued.

It is important to note that the measurements of intraabdominal pressure during laparoscopy have significant limitations. During the course of these studies, it was often observed that repeat stimulation at the same site on the diaphragmatic surface often resulted in widely varying...
pressure levels. Small variations in the degree of abdominal insufflation, which can occur during the course of the procedure, most likely altered diaphragm length, which is an important determinant of force generation.20

**Interaction Between Left and Right Hemidiaphragm Contraction**

In each subject, inspired volumes resulting from bilateral diaphragm contraction were substantially greater than the arithmetic sum of left and right hemidiaphragm contraction alone, indicating a synergistic effect. This occurred both during maximum diaphragm stimulation and also with lower stimulus frequency, long-term pacing parameters. This same effect also was observed qualitatively by Glenn et al6 with conventional PNP. The mechanism of this phenomenon most likely relates to the retraction of the flaccid hemidiaphragm into the thorax as a result of the negative pressure generated by the contraction of the opposite hemidiaphragm. The greater the compliance of the noncontracting hemidiaphragm, the greater the degree of synergism. The clinical correlate of this phenomenon includes patients with unilateral diaphragm paralysis who experience dyspnea that is related to the retraction of the paralyzed diaphragm into the thorax and derive significant benefit from diaphragm plication.21

**Side Effects**

While much less invasive than a thoracotomy, laparoscopic surgery also has some associated risks.21–23 In addition to complications common to all surgical procedures, laparoscopy may be associated with the development of pneumothorax and subcutaneous emphysema. Pneumothorax is thought to develop from the movement of gas from the peritoneal cavity to the pleural space via the mediastinum through tissue planes or congenital diaphragmatic defects and usually resolves spontaneously.23 One of the subjects in the present study had a pneumothorax that may have developed by one of the above-mentioned mechanisms or by air tracking along openings in the diaphragmatic surface created by electrode placement. Although this subject was asymptomatic and had normal levels of oxygenation, the pneumothorax was evacuated by chest tube drainage, since the pneumothorax was slow to resolve and the subject was ventilator-dependent.

One subject developed right shoulder pain during the maximum stimulation of a single electrode. This most likely occurred as a consequence of the stimulation of phrenic nerve afferents. His symptoms were completely alleviated by a modest reduction in stimulus current. Another subject developed hay fever symptoms, which were a common problem prior to his injury but had not been present when he was receiving mechanical ventilation. The restoration of nasal airflow during diaphragmatic pacing evidently resulted in the recurrence of symptoms. One subject had intermittent aspiration of food during meals, which most likely was related to the large negative airway pressure generated during contraction of the diaphragm. This problem was eliminated by use of a Passy-Muir valve during meals. This device served to reduced the magnitude of negative pressure in the oropharynx. Other potential long-term effects of prolonged pacing include electrode dislodgement and electrode breakage, either of which could result in inadequate inspired volume generation.

**Table 3—Effects of Bilateral Long-term Pacing on Inspired Volume Production and Maximum Time Without Ventilatory Support**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Pacing Duration, h</th>
<th>Inspired Volume During Chronic Pacing, mL</th>
<th>Stimulus Frequency During Chronic Pacing, Hz</th>
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<tr>
<td>1</td>
<td>24</td>
<td>800</td>
<td>15</td>
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<tr>
<td>5</td>
<td>24</td>
<td>850</td>
<td>18</td>
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</table>

*Maximum achieved.
Future Developments

The current system requires electrode wires that exit the skin and are connected to an external power generator. These wires carry a small risk of infection and represent a significant inconvenience. Current investigations are underway to develop a totally implantable system such as the radiofrequency-powered pulse generators, which are currently utilized with conventional PNP and combined intercostal and diaphragm pacing systems.

Combined intercostal and diaphragm pacing systems are also successful in maintaining long-term ventilatory support in patients with only a single functional phrenic nerve. Rather than direct PNP, it is possible that combined intercostal and unilateral phrenic nerve stimulation also can be achieved by IM diaphragm pacing, eliminating the need for a thoracotomy and for manipulation of the phrenic nerves in these subjects as well.

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Severe Autoimmune Hemolytic Anemia Treated by Paralysis, Induced Hypothermia, and Splenic Embolization*

Ronna Campbell, MD, PhD, and Paul E. Marik, MD, FCCP

Autoimmune hemolytic anemia (AIHA) is the clinical condition in which IgG antibodies bind to RBC surface antigens and initiate RBC destruction via the complement and reticuloendothelial system. AIHA is commonly treated with transfusions, corticosteroids, and splenectomy. We present a case of an adult with life-threatening AIHA secondary to ulcerative colitis emergently managed with neuromuscular paralysis, induced hypothermia, and splenic embolization. (CHEST 2005; 127:678–681)

Key words: autoimmune hemolytic anemia; hypothermia; liver transplantation; splenic embolization; ulcerative colitis

Abbreviations: AIHA = autoimmune hemolytic anemia; LDH = lactate dehydrogenase; OPSI = overwhelming postsplenectomy infection; PRBC = packed RBC; VO₂ = oxygen uptake

A utoimmune hemolytic anemia (AIHA) is the clinical condition in which IgG antibodies bind to RBC surface antigens and initiate RBC destruction via the complement and reticuloendothelial system. Since the auto-antibodies are usually directed against high-incidence antigens, they often exhibit reactivity against allogenic RBCs as well. AIHA is an uncommon disease, with an incidence of approximately 10 cases per million population. AIHA occurs more commonly in women than in men and usually occurs in midlife. Approximately 50% of cases are primary AIHA, the remaining 50% being associated with an underlying disease, most commonly lymphoproliferative and connective tissue disease. AIHA can also be induced by drugs. AIHA is rarely associated with ulcerative colitis, occurring in approximately 0.6 to 1.7% of cases. Because the severity of AIHA may range from indolent to acutely life threatening, the impetus to initiate treatment must begin with a thorough appraisal of symp-toms and the severity of hemolysis. Rapidly developing anemia with a hematocrit of < 20 requires urgent management. AIHA is commonly treated with transfusion, corticosteroids, and splenectomy. Treatments for refractory anemia include immunosuppressive agents, IV Ig, plasma exchange, and danazol, which may have limited efficacy and delayed onset of action. We present a case of an adult with life-threatening AIHA secondary to ulcerative colitis emergently managed with neuromuscular paralysis, induced hypothermia, and splenic embolization.

CASE REPORT

A 43-year-old woman, status-post total colectomy in 1991 for ulcerative colitis and orthotopic liver transplant in 1999 for sclerosing cholangitis, was transferred from an outside hospital with a 2-day history of nausea and vomiting and 1-day history of jaundice. Physical examination revealed intact mental status, jaundice, and pallor. CBC count revealed a hemoglobin of 4.6 g/dL with a reticulocyte count of 42.5%, a WBC count of 17.2 × 10⁹/L, with 68% neutrophils and 12% bands, and a platelet count of 368 × 10⁹/L. Spherocytes were present on peripheral smear. Blood chemistry revealed increased total bilirubin of 5.5 mg/dL (< 0.1 mg/dL conjugated bilirubin) and lactate dehydrogenase (LDH) of 922 IU/L. Serum haptoglobin was < 5.0 mg/dL. The direct antiglobulin test (direct Coombs test) was positive for C3 and IgG. A diagnosis of severe AIHA was made. The patient was started on oral corticosteroids (prednisolone, 60 mg/d), and cross-matched blood was ordered. Due to the presence of alloantibodies and autoantibodies, it was extremely difficult to find blood for the patient.

On the second day of hospitalization, the patient became symptomatic secondary to tissue hypoxia. Physical examination revealed tachycardia (120 to 130 beats/min), tachypnea (20 to 26 breaths/min), mild hypotension (100/53 mm Hg), temperature of 37.4°C, and a markedly depressed level of consciousness. CBC count showed hemoglobin of 3.3 g/dL, and blood chemistry revealed a lactate level of 6.2 mg/dL. At this time, the patient was urgently admitted to the liver transplant ICU. She was intubated and placed on mechanical ventilation (fraction of inspired oxygen, 100%). In order to decrease oxygen uptake (VO₂), the patient was sedated and paralyzed (with propofol and vecuronium) and actively cooled with a cooling blanket and cooled IV crystalloids. In addition, the patient received 1 g of methylprednisolone IV. Secondary to these interventions, the patient’s pulse rate decreased to the upper 80s, temperature decreased to 33.5°C, BP decreased slightly to 90/53 mm Hg, and lactate level decreased to 1.0 mg/dL. The patient was then slowly transfused with 1 U of blood, crossed-matched as closely as possible, when it became available later in the day. The hemoglobin level subsequently increased to 3.9 g/dL, and LDH further increased to 1,058 IU/L. Given the severity of the AIHA and the paucity of blood available for transfusion, it was decided that the patient would likely benefit from splenic embolization.

Embolization of the splenic artery, with polyvinyl alcohol particles, was performed the following day in the interventional radiology suite. The patient tolerated the procedure well. On the day of the splenic embolization, the patient subsequently received three more units of packed RBCs (PRBCs). The hemoglobin level increased to 9.4 g/dL (hematocrit 26.5), and LDH increased to 2,333 IU/L. Following the blood transfusion, the neuromuscular blocking agent was discontinued and the propofol gradually weaned off. The patient was extubated the following day. The patient's temperature, hemoglobin concentration, LDH, and lactate levels over this time period are illustrated in Figure 1. After extubation, the patient complained of abdominal...