Extended use of diaphragm pacing in patients with unilateral or bilateral diaphragm dysfunction: A new therapeutic option

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Background. Diaphragm dysfunction (DD) can cause sleep abnormalities, dyspnea, atelectasis, and respiratory failure. Historical treatments, including positive pressure ventilation or diaphragm plication, may alleviate symptoms but do not restore physiologic diaphragm function. Diaphragm pacing (DP) is approved for spinal cord–injured patients and in amyotrophic lateral sclerosis. We report a series of DD patients undergoing use of DP outside of these initial indications.

Methods. This report involves a prospective, nonrandomized, interventional trial under institutional review board approval at a single institution. DP involves laparoscopic motor point mapping with implantation of intramuscular electrodes in each hemidiaphragm. Postoperatively, diaphragm conditioning ensues.

Results. Twenty-seven patients were evaluated; all patients had symptomatic and objective hypoventilation for an average of 36 months of symptoms. Causes included idiopathic (n = 13), chest surgery (n = 5), shoulder surgery or trauma (n = 6), and others (n = 3); 17 had bilateral involvement, 6 had nonstimulable diaphragms and were not implanted, and 21 were implanted. Thirteen (62%) had substantial clinically relevant respiratory improvements. Four ventilator patients were weaned completely. Four had partial improvement, 3 had no improvement, and 1 patient was lost to follow-up for objective analysis.

Conclusion. This is the first report of DP being used to treat diverse causes of DD. Eighty-one percent of implanted patients experienced improvements. This success suggests a potential for a wider use of DP and areas for future research. (Surgery 2014;156:776-86.)

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The diaphragm is the primary muscle of respiration. It is innervated by the phrenic nerve that is composed of nerve roots arising from C3 to C5. Disease processes that affect diaphragm innervation or contraction can cause either unilateral or bilateral diaphragm dysfunction (DD). Unilateral DD can be asymptomatic, presenting with an incidental chest radiographic finding or have mild, sleep-related symptoms, or even clinically important dyspnea with continued diaphragm elevation, paradoxic movement, and atelectasis. Bilateral DD can lead to respiratory failure and dependence on mechanical ventilation. The incidence of DD, either unilateral or bilateral, is difficult to quantify because of the multiple causes and potential conflicts of interest.

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ventilation with noninvasive positive-pressure therapy or diaphragm plication for unilateral DD. None of these therapies address the cause or provide therapy to the phrenic nerve or the diaphragm to help in recovery. Diaphragm pacing (DP) using the NeuRX system (Synapse Biomedical, Oberlin, OH) is a percutaneous electrode system where 2 electrodes are placed laparoscopically into each hemidiaphragm at the point of mapped maximal contraction in patients with intact phrenic nerves and cervical motor neurons. DP is proven therapy for patients with spinal cord injury to provide complete diaphragm ventilation removing them from mechanical ventilation. In patients with amyotrophic lateral sclerosis (ALS [Lou Gehrig’s disease]), DP conditions the diaphragm and delays the need for mechanical ventilation and death. We report our initial experience in a series of patients outside of these initial indications undergoing successful laparoscopic evaluation and subsequent use of DP to treat isolated DD.

PATIENTS AND METHODS

This was a single-institution, retrospective analysis of a prospective, nonrandomized, interventionional experience approved by our institutional review board (number 02-10-18). This is a compassionate use implantation under a Food and Drug Administration humanitarian device exemption for a humanitarian use device. All patients gave informed consent for both the evaluation and subsequent operative mapping and implantation, and compliance with the Health Insurance Portability and Accountability Act of 1996 was met. Patients also understood that electrodes would not be implanted if the diaphragm was not stimulable, and then they would be considered for diaphragm plication. Demographic data, operative data, and postoperative data were assessed prospectively then analyzed retrospectively. All patients had, at minimum, chest radiographs. Attempts were made to obtain pulmonary function tests, sniff fluoroscopy, arterial blood gases, and PNCS measuring compound muscle action potential amplitudes and latencies as we described previously.

Patients underwent diagnostic laparoscopy, and their diaphragms were assessed for the ability to respond to extrinsic stimulation. The operation has been described previously, but is reviewed briefly herein with specific comments concerning DD patients. A supraumbilical, midline access port is placed higher than in standard patients so that the elevated diaphragm can be visualized. Two 5-mm, lateral, subcostal trocars were then placed to assess the diaphragms. A standard laparoscopic dissector was attached to an external clinical station that provides electrical stimulation. Initially, a twitch of stimulation was delivered to see if there was movement of the involved diaphragm. In patients with unilateral involvement, this was compared with the contralateral asymptomatic side. If there was no movement, a train of electrical current was applied over 1 second. Additionally, stimulation parameters may be increased to the highest setting. When no diffuse diaphragm movement is observed, the abdominal pressure is decreased, and the stimulation trial is repeated. If there is no diaphragm movement, the procedure is terminated. In our experience with ALS patients, this protocol identifies intact motor units. There is no benefit in stimulating a completely denervated muscle.

If the diaphragm is stimulable, the falciform ligament is divided, and a 12-mm epigastric trocar is placed to accommodate the 11-mm diameter implant instrument. The diaphragms are mapped to identify the motor point where maximal contraction occurs, and 2 electrodes are implanted in each diaphragm (Fig 1). The electrodes are tunneled from the epigastric port to an exit site along with a subcutaneous ground electrode. Postoperatively, the external DP pulse generator is programmed to maximize electrical stimulation through each electrode with pulse width, amplitude, frequency, and breaths per minute while maintaining patient comfort. The patient begins a program of diaphragm conditioning by increasing utilization of DP with 30-minute sessions several times a day to full-time use as soon as tolerated. The experience in ALS patients has shown that noninvasive positive pressure ventilation suppresses diaphragm activity. Suppressed diaphragm activity leads rapidly to diaphragm atrophy and conversion of the good, slow twitch-type, I muscle fibers to less functional fast, twitch-type IIb fibers. Therefore, patients dependent on noninvasive positive pressure ventilation or tracheostomy mechanical ventilation will always use DP whenever they are on noninvasive positive pressure ventilation or tracheostomy mechanical ventilation. In patients on tracheostomy mechanical ventilation, a weaning process is begun similar to the process described for patients with spinal cord injury of gradually increasing time on DP and decreasing ventilator support.

Diaphragm electromyography (dEMG) has been described previously but has been of limited use because of the difficulty and reproducibility of
measuring it transcutaneously or the safety and difficulty of direct needle dEMG. The DP electrode system has the ability to not only stimulate the diaphragm, but gives us the unique opportunity to study the intramuscular dEMG of the implanted electrodes consistently and continuously when not pacing. A polysomnography unit (Crystal PSG, CleveMed, Cleveland, OH) is used to record dEMG measurements by assessing the spatial summation between 9 mm of exposed intramuscular electrodes in each hemidiaphragm using the implanted remote subcutaneous electrode as the ground. This allows continuous evaluation of epochs of diaphragm activity with normal respiration, maximum respiration during sleep, or when noninvasive positive pressure ventilation or tracheostomy mechanical ventilation was being utilized. This system can identify control problems of each hemidiaphragm separately, and the size or amplitude of the burst activity correlates with the strength of diaphragm contraction.13 The assessment of this dEMG was the primary mode of assessing recovery and function of the diaphragm in this report.

Patients were followed postoperatively for objective evidence through dEMG of diaphragm recovery, weaning from noninvasive positive pressure ventilation or tracheostomy mechanical ventilation, and PFTs. Patients were considered to be improved if they had both objective improvement in the dEMG and 1 additional objective respiratory improvement (2 stars on Table I). Partial success (1 star on Table I) occurred if there was minor objective improvement in the dEMG even if there were other objective tests. The primary endpoint of success was recovery of diaphragm burst activity. No evidence of improvement was a failure. Long-term use or removal of DP electrodes was also followed.

RESULTS

Twenty-seven patients were evaluated from 2010 to 2013 with an average age of 55 years (range, 19–78). All patients had abnormal chest radiography. The average time with symptoms for the entire group was 36 months (range, 0.5 months to 10 years). For those patients with PFT results, the average FVC was 59% predicted (range, 24–96%). The average maximal inspiratory pressure was 35 mmHg (range, 22–68). The patients were grouped into 4 categories: Idiopathic (n = 13), chest surgery (n = 5), shoulder surgery or trauma (n = 6), and other (n = 3). Seventeen had bilateral involvement. Laparoscopic evaluations showed 6 with nonstimulable diaphragms. Twenty-one patients were implanted with subsequent diaphragm conditioning. Table I summarizes the results for those patients implanted with DP, and Table II summarizes the results for patients with nonstimulable diaphragms at laparoscopy.

There were no relationships between successful and nonsuccessful subjects with respect to preoperative findings using a Chi-square statistic in a cross-tabulation analysis to quantify the degree of association between variables (including age, duration of symptoms, PNCS, FVC, maximal inspiratory pressure, noninvasive positive pressure ventilation, tracheostomy mechanical ventilation, or pCO2). The average age for implanted patients was 51 years (range, 19–73); for nonimplanted patients, it was 68 years (range, 52–78). The average duration of time with symptoms was 41 months (range, 0.5–120) for those implanted, whereas for those not implanted the average duration was 22 months (range, 5–36). Four patients could not undergo PNCS because of central lines or technical difficulties in obtaining PNCS (3 were on tracheostomy mechanical ventilation). Two of the 6 nonimplanted patients had recordable the average compound muscle action potentials on PNCS yet had nonstimulable diaphragms, considered false positives. Of the patients implanted, 10 had absent compound muscle action potentials on PNCS yet had nonstimulable diaphragms at laparoscopic mapping, considered false negatives. Of the patients implanted, 10 had absent compound muscle action potentials on PNCS but had stimulable diaphragms, categorized as false-negative studies. Four of the non–DP-implanted patients had unilateral involvement with 3 undergoing diaphragmatic plication. The plicated group had
Table I. Demographic, preoperative and postoperative results of patients implanted

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Mechanism</th>
<th>Symptoms (Months)</th>
<th>Paradoxical movement</th>
<th>PNCS</th>
<th>FVC</th>
<th>MIP</th>
<th>NIV/ TMV</th>
<th>pCO₂</th>
<th>Post implant dEMG changes</th>
<th>Objective Improvements</th>
<th>Result</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>55</td>
<td>Lobectomy</td>
<td>43</td>
<td>R</td>
<td>Yes</td>
<td>NR</td>
<td>R</td>
<td>+L</td>
<td>94</td>
<td>86</td>
<td>NIV</td>
<td>32</td>
<td>Increase burst and control activity</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>CABG with bilateral IMA resection</td>
<td>1</td>
<td>B</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
<td>TMV</td>
<td>37</td>
<td>Increase burst and control activity</td>
<td>Weaned from ventilator</td>
<td>++</td>
<td>Removed</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>58</td>
<td>Myxoma resection</td>
<td>5</td>
<td>B</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
<td>TMV</td>
<td>36</td>
<td>Excellent bilateral recovery</td>
<td>Weaned from ventilator</td>
<td>++</td>
<td>Removed</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>64</td>
<td>Cardiac transplant</td>
<td>2</td>
<td>B</td>
<td>No</td>
<td>n/a</td>
<td>32</td>
<td>n/a</td>
<td>NIV</td>
<td>44</td>
<td>Increase burst bilaterally</td>
<td>↑ diaphragm excursion-2 cm</td>
<td>++</td>
</tr>
</tbody>
</table>

| Shoulder surgery or trauma | | | | | | | | | | | | | |
| 5 | F | 70 | Rotator cuff surgery | 24 | R | Yes | NR | R | +L | 78 | 42 | NIV | 37 | Increased burst activity | Off O₂; resolution of paradoxical motion | ++ | Still DP |
| 6 | M | 33 | Shoulder trauma | 36 | R | No | + R | +L | 60 | 24 | NIV | 36 | n/a | Some minor activity on R | n/a | n/a | Unknown |
| 7 | M | 57 | Rotator cuff surgery | 48 | R | Yes | + R and +L | n/a | 68 | NIV | 45 | None | Improved MIP | ++ | Deceased |
| 8 | M | 48 | Neck trauma | 108 | B | No | NR | R | NR | L | 31 | 30 | NIV | n/a | Increased burst activity | None | Ø | Removed |
| 9 | M | 44 | Chest trauma | 120 | B | No | NR | R | NR | L | 85 | 34 | NIV | n/a | Improved MIP | None | Ø | Removed |

| Idiopathic | | | | | | | | | | | | | |
| 10 | M | 30 | Idiopathic | 24 | B | No | + R | NR L | 50 | 19 | NIV | 33 | Increased burst activity | Improved diaphragm movement | + | Unknown |
| 11 | M | 73 | Idiopathic | 96 | B | No | NR | R | NR | L | 29 | 38 | NIV | 39 | No recovery | None | Ø | Removed |
| 12 | F | 60 | Idiopathic | 72 | B | No | NR | R and +L | 53 | 24 | 33 | Increased burst activity | ↓ desaturations during sleep | ++ | Still DP |
| 13 | F | 49 | Idiopathic | 48 | B | Yes | + R | +L | 96 | n/a | NIV | 38 | Mild burst activity | Off O₂; Improved 6 min walk | + | Still DP |
| 14 | M | 44 | Idiopathic | 8 | B | No | + R | +L | 32 | 39 | NIV | 37 | Mild burst activity improvement | None | Ø | Removed |
| 15 | F | 50 | Idiopathic | 11 | L | No | + R | +L | 59 | 72 | None | n/a | Mild burst activity | No changes in symptoms | Ø | Removed |
| 16 | M | 62 | Idiopathic | 12 | R | Yes | NR | R | +L | 77 | n/a | None | n/a | Significant improvement burst activity | Improved diaphragm movement with DP, less elevated | ++ | Still DP |

(continued)
some improvement in shortness of breath. No other patient in the nonstimulable group had any improvement in their condition.

In the 21 DP implanted group, 13 (62%) had clinically relevant respiratory improvements and 4 patients dependent on tracheostomy mechanical ventilation weaned completely from the ventilator with DP. Four patients (19%) had partial improvements, whereas 3 (14%) showed no improvement. One patient (subject 6) was unable to follow-up for any objective testing and was excluded even though he reported that he felt less short of breath subjectively.

In the first category of Table I (4 patients with a presumed phrenic nerve injury during a thoracic operation), all patients had clinically relevant improvement. Two patients dependent on tracheostomy mechanical ventilation were weaned using DP. Their percutaneous DP electrodes were removed by pulling them taunt at the skin and cutting the electrodes at the exit site of the skin, similar to removing epicardial pacing wires. The implanted electrodes could also be used to follow recovery of the patient’s phrenic nerve as identified in Fig 2. The cardiac transplant patient had substantial improvement in diaphragm burst activity and required less use of positive pressure ventilation. This patient is still using DP; she is <1 year postimplantation. The only patient (#1) who had had unilateral involvement for 43 months had resolution of paradoxical movement with DP. This patient still has loss of automatic control of the diaphragm and uses DP to maintain the effects.

The next category of patients (shoulder surgery or trauma in Table I) most likely sustained damage to the phrenic nerve roots either from anesthetic shoulder blocks performed during rotator cuff surgery or stretch injuries from trauma. Three patients had complete resolution of their symptoms, and 2 had the electrodes removed. One of these patients with successful DP died of unrelated cardiac issues. In the 2 patients with minimal or no improvement, there was positive preoperative PNCS, and they had symptoms for less time than the patients with success in this group.

The largest group of 9 patients falls under the category of unknown or idiopathic DD with symptoms ranging from 1.5 to 96 months. Only 2 had unilateral involvement. Four patients had clinically relevant recovery, including 1 patient requiring tracheal mechanical ventilation who had hypercarbia before tracheostomy. This patient had complete recovery, normalized pCO$_2$, and completely normalized diaphragm burst activity before electrode removal. Three patients in this category

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Mechanism</th>
<th>Symptoms (Months)</th>
<th>Side</th>
<th>Paradoxical movement</th>
<th>Objective Improvements</th>
<th>Result</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>M</td>
<td>64</td>
<td>Idiopathic</td>
<td>42</td>
<td>B</td>
<td>No</td>
<td>+</td>
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</tr>
<tr>
<td>18</td>
<td>M</td>
<td>63</td>
<td>Idiopathic</td>
<td>37</td>
<td>B</td>
<td>No</td>
<td>+</td>
<td>Removed</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>36</td>
<td>Diaphragm flutter, phrenic nerve crush</td>
<td>120</td>
<td>B</td>
<td>No</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>42</td>
<td>Charcot-Marie-Tooth</td>
<td>1</td>
<td>B</td>
<td>No</td>
<td>+</td>
<td>Removed</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>19</td>
<td>Spinal muscle atrophy</td>
<td>55</td>
<td>B</td>
<td>No</td>
<td>+</td>
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<td></td>
</tr>
</tbody>
</table>

Table I. (continued)

- Paradoxical movement
- Objective Improvements
- Result
- Status
- NIV, noninvasive ventilation; TMV, tracheostomy mechanical ventilation; PNCS, phrenic nerve conduction studies; MIP, maximal inspiratory pressure; FVC, % predicted of forced vital capacity; IMA, internal mammary artery; L, left; R, right; O2, oxygen; CABG, coronary artery bypass graft; dEMG, diaphragm electromyography; FC, % predicted of forced expiratory volume in 1 second.
had partial improvements. The 2 patients with no improvement had their electrodes removed easily.

The last category in Table I includes 3 patients with substantial bilateral DD for other described disease entities and DP had a positive effect. Patient 19 had severe diaphragm flutter also known as belly dancer syndrome. At an outside institution, she had a left phrenic nerve crush procedure, leaving her with an injured, nonfunctional left phrenic nerve and left diaphragm paradoxical movement. She continued to have intermittent severe diaphragm flutter. DP stimulation helped in complete recovery of her left diaphragm. Additionally, utilizing DP at low settings caused suppression of diaphragm flutter.

Patient 20 had Charcot–Marie–Tooth disease. This hereditary neuropathy affects both sensory and motor nerves and is caused by axon and/or myelin sheath dysfunction and rarely causes respiratory failure. This patient had marked respiratory compromise with a FVC of only 24% predicted with hypercarbia. She had a stimulable diaphragm and continues pacing with no objective improvement in dEMG on follow-up, but her rate of decline of FVC has decreased.

Patient 21 had spinal muscle atrophy, which is often associated with respiratory failure at a young age or later in life. This disorder is inherited and results in the loss in lower motor neurons, including the continued loss of diaphragm motor units resulting in respiratory failure. Therefore, the diaphragm at the late stage of the disease would not be stimulable. In this case, the patient was having progressive respiratory problems with hypercarbia. Aspiration during a routine wisdom tooth extraction led to dependence on tracheal mechanical ventilation. At laparoscopy, this patient demonstrated prompt and robust diaphragmatic response to pacing that allowed adequate tidal volumes for rapid weaning from mechanical ventilation. Analysis of postimplantation dEMG also identified a component of central hypoventilation that was corrected by DP.

DISCUSSION

Symptomatic unilateral or bilateral DD has no specific therapies besides allowing time for reinnervation or diaphragm plication for unilateral DD. Growing evidence suggests that even unilateral DD can have clinically relevant effects on sleep.14,15 These patients who were thought previously to be asymptomatic may benefit from other therapies. This is the first report of DP being successful in treating DD in patients who do not have spinal cord injuries or ALS. Eighty-six percent of patients obtained improvements with implantation of DP if they had a stimulable diaphragm. For patients with spinal muscle atrophy, Charcot–Marie–Tooth disease, and diaphragm flutter, DP may provide a new, alternative therapy. This report highlights the ability of the implanted electrodes to be used to not only condition the diaphragm, but to monitor recovery of the patient’s diaphragm. DP allows new ways to assess diaphragm function and respiratory physiology.

The basis for this exploration of DP in DD was the experience in neuralgic amyotrophy (Parsonage–Turner syndrome or brachial plexus

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Mechanism</th>
<th>Months of symptoms</th>
<th>Side</th>
<th>Paradoxical movement</th>
<th>PNCS</th>
<th>FVC</th>
<th>MIP</th>
<th>NIV or TMV use</th>
<th>Long-term outcome</th>
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<tr>
<td>1</td>
<td>M</td>
<td>78</td>
<td>Chest CABG and asbestos</td>
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<td>NR R</td>
<td>NR L</td>
<td>47</td>
<td>53</td>
<td>NIV</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>Trauma</td>
<td>36</td>
<td>R</td>
<td>No</td>
<td>NR R</td>
<td>+ L</td>
<td>38</td>
<td>32</td>
<td>NIV</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>76</td>
<td>Idiopathic</td>
<td>24</td>
<td>B</td>
<td>No</td>
<td>NR R</td>
<td>NR L</td>
<td>47</td>
<td>42</td>
<td>TMV</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>Idiopathic</td>
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<td>B</td>
<td>No</td>
<td>+ R</td>
<td>+ L</td>
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<td>n/a</td>
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</tr>
<tr>
<td>5</td>
<td>F</td>
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<td>5</td>
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<td>NR R</td>
<td>+ L</td>
<td>64</td>
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<td>6</td>
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<td>Yes</td>
<td>+ R</td>
<td>+ L</td>
<td>52</td>
<td>32</td>
<td>No</td>
</tr>
</tbody>
</table>

B, Bilateral; CABG, coronary artery bypass grafts; FVC, % predicted of forced vital capacity; L, left; MIP, maximal inspiratory pressure; n/a, not available; NIV, noninvasive ventilation; NR, nonreactive; PNCS, phrenic nerve conduction studies; R, right; TMV, tracheostomy mechanical ventilation.
neuritis), and the use of electrical stimulation in the rehabilitation of muscles and injured nerves. In neurologic amyotrophy, there is a sudden weakness of the upper extremity from an autoimmune damage to the nerve roots of the brachial plexus. Physical therapy is the primary mode of therapy with recovery in 75% of patients in 2 years. EMG of the upper extremity is used to

Fig 2. Subject 2 with phrenic and diaphragm dysfunction after internal mammary artery graft to the coronary artery caused by a presumed vascular insult to the nerve. The EKG tracing is marked with an arrow and the diaphragm burst activity is circled. (A) Left dEMG shows little activity of the diaphragm muscle during volitional breathing early after implantation. The recorded amplitude is only 175 uv. (B) Recovery of dEMG burst activity seen before electrode removal showing an increase in amplitude of diaphragm burst activity to 1,499 uv. The amplitude or size had been followed through the recovery showing a gradual return to this point.
monitor recovery, which was the reason we monitored dEMG in this report. In rehabilitation medicine, muscle electrical stimulation has been shown to prevent muscle atrophy, improve muscle thickness, improve muscle strength, and improve nerve recovery.17,18

In patients with DD, not only is there muscle atrophy, but there is elongation of the diaphragm with sarcomere damage owing to either the paradoxical effect of the good diaphragm or the unopposed abdominal pressure and abdominal contents pushing both diaphragms up. This stretching of the diaphragm may also affect the ability for recovery of the respiratory system. DP would be considered the physical therapy that helps in neuralgic amyotrophy or the electrical stimulation that has been proven to help in recovery from other nerve injuries. In summary, we hypothesized that the use of DP in this diverse group of DD includes conditioning the diaphragm to type I muscle fiber, preventing muscle atrophy, improving diaphragm thickness,6 and helping with neural recovery.

There are potential limitations to this report. The limitations include the retrospective analysis without a control population, nonuniform data collection, and selection bias based on the single-site analysis. An untreated control population matched with similar deficits, etiologies, and demographics would have been desirable, but was impractical given the unique nature of these relatively infrequent and unique situations. We cannot exclude the possibility that in some cases improvements could have occurred spontaneously. Gayan–Ramarez et al19 reported that 52% (12/23) patients with DD recovered after 2 years. The average duration of symptoms in our implanted patients was 41 months, well beyond the time reported for spontaneous recovery. In addition, 8 patients had symptoms for <1 year, with 7 showing improvement with DP. Also, none of our patients who were found to have a completely denervated diaphragm had any spontaneous recovery of diaphragm function, with the only option of having a diaphragm plication.

Our patients with unilateral DD were also not compared with an alternative therapy, such as diaphragm plication, which is often performed on patients with unilateral DD. Because of the referral pattern, only 10 of our patients (37%) had unilateral involvement, which is less than the usual presentation of 70% unilateral. Diaphragm plication works presumably through immobilization of the diaphragm with subsequent decrease in paradoxical movement. Plication has been reported to improve vital capacity by ≤20% with improvement of dyspnea in some patients.20

Recovery of phrenic nerve function after injury can be a prolonged process. Currently, a preoperative observation for ≥2 years after the onset of symptoms is recommended before considering plication because of this potential delay in phrenic nerve recovery. In this study, we have seen recovery of dEMG owing to the use of DP much past this 2-year time period, suggesting that this system may have additional benefits. A functioning diaphragm is better than a fixated diaphragm; therefore, if these findings can be duplicated, then DP should be attempted before plication at any duration of time with symptoms, because plication destroys the architecture of the diaphragm preventing future recovery. Also, early laparoscopic evaluation of the diaphragm would allow placement of DP if the diaphragm is stimulable, which may hasten recovery or if the diaphragm is denervated, early use of diaphragm plication may be reasonable. This early diaphragm assessment is now being done for patients with spinal cord injury as described by Poslusny et al.3

PNCS are performed routinely to identify if the phrenic nerves are intact but, as highlighted in this report, PNCS may not have a positive predictive value in this patient population. In 10 of 21 patients implanted, 9 had unevolvable compound muscle action potentials on PNCS, yet DP was able to cause improvements in respiratory function. In contrast, 2 patients who had compound muscle action potentials on PNCS were not implanted, because there was no functional diaphragm with stimulation at laparoscopic mapping. The surface electrodes in PNCS assess primarily anterior diaphragm. Posterior diaphragm contractions, however, are more important for ventilation; the area stimulated directly during the laparoscopic mapping of the diaphragm in DP is the posterior diaphragm. Although PNCS are routinely performed preoperatively, the more appropriate assessment is carried out during laparoscopic mapping with direct analysis of the diaphragm.

There are several examples in these series of cases that deserve specific mention. Spinal muscle atrophy primarily involves a loss of lower motor neurons. Respiratory failure was thought to be owing to the resulting loss of the motor units with a subsequent nonstimulable diaphragm. In this case the diaphragm had strong contractions but there was a loss of neural control of respiration and an acquired central sleep apnea identified by dEMG analysis. If this finding can be duplicated in other patients with spinal muscle atrophy, this may
significantly change the management of this disease and other pediatric neuromuscular diseases.

Phrenic nerve injury during a cardiac or lung transplant can have marked deleterious effects because of the immunocompromised state of the patient and the resulting risks of pneumonia. In the cardiac transplant patient, there was considerable improvement after DP, which has led to a planned prospective evaluation of implanting the DP electrodes during the initial chest procedure. If the patient does well, then the electrodes can be pulled, in a manner similar to the temporary epicardial pacing wires; if the patient has any diaphragm abnormalities then DP can be initiated.

In conclusion, this is the first report of DP being used successfully to treat DD in selected patients without spinal cord injury or ALS. Unfortunately, functional respiratory recovery cannot be predicted with accuracy from the preoperative clinical evaluation, and intraoperative mapping of the diaphragm is often necessary. DP may have a positive effect even years after symptoms develop. The utility of using the implanted electrodes as an assessment tool, as well as therapeutic device, allows for ongoing diagnostics and expansion of research across multiple medical conditions.

REFERENCES


DISCUSSION

Dr William Cirocco (Columbus, OH): The authors are to be commended for leading a multi-institutional study that directly contributed to the approval of diaphragm pacing for the management of patients with bilateral diaphragm dysfunction owing to spinal cord injury and amyotrophic lateral sclerosis (ALS). This is the first report of attempts to use diaphragm pacing to treat diaphragm dysfunction of patients without spinal cord injury or ALS.

Patients with diaphragm dysfunction underwent a battery of pulmonary testing preoperatively to confirm diaphragm dysfunction, followed by...
laparoscopic motor point mapping with implantation of intramuscular electrodes into each stimulable hemidiaphragm at the point of maximal contraction in patients with intact phrenic nerves and cervical motor neurons.

Of the 21 patients implanted, 13 (62%) had significant respiratory improvement, 4 were able to be weaned off the ventilator, and 5 (23%), had partial improvement, for total of 86% of patients showing improvement, with 3 patients (14%) having no improvement.

The results certainly warrant further research into potential expansion for the role of diaphragm pacing for patients with diaphragm dysfunction, including Charcot-Marie-Tooth, spinal atrophy, and diaphragm flutter.

I have 3 questions. First, how are these patients selected? Were there any exclusion criteria, such as age, extent of disease, disability, or disease duration?

Second, the good slow twitch-type 1 muscle fibers covert rapidly to less functional fast twitch-type 2b fibers. Therefore, diaphragm pacing should be considered early in diaphragm dysfunction, but can diaphragm pacing reverse this process and convert the type 2b muscle fibers back to type 1?

And last, given that almost 50% of patients (10 out 21) had false-negative phrenic nerve conduction studies, combined with 2 out of 6 who had false-positive phrenic nerve conduction studies, what should be the role, if any, of phrenic nerve conduction studies as an exclusion or exclusion criterion for patients with diaphragm dysfunction under consideration for diaphragm pacing going forward?

Dr Raymond P. Onders (Cleveland, OH): The selection criteria were just patients who showed up into our diaphragm pacing clinic. We have a clinic for diaphragm pacing, mostly for spinal cord injury and ALS. So that is probably our biggest selection bias. These were patients who were motivated, knew they had a problem. That is probably one of our concerns for this, because it is not all comers, it is patient who actually made it to us and actually agreed to undergo the surgery. So that is our problem. Obviously, in a multicenter trial, we would be able to help control for that. So it is just patients who showed up.

You are exactly right on muscle fiber type. A lot of the ventilator-induced diaphragm dysfunction, the *New England Journal of Medicine* article from 4 years ago, showed that we get conversion to nonfunctional type 2b muscle fiber within hours of being on a ventilator. You lose 50% of your diaphragm muscle mass within 12 hours of being on a ventilator. Diaphragm pacing—and I know Tom Stellato is in the audience—and I know he has been working on the phrenic nerve conduction study when you have central lines, it is a contraindication for that, we actually found in that article that knowing that the diaphragm is dead significantly changes your management of those patients. Therefore, you can stop all weaning trials if you cannot stimulate the diaphragm.

So we kind of feel, and I think with our new use in trauma, it is just going to surgery early laparoscopically may be the way to go.

Dr Scott Melvin (New York, NY): Besides the patient either getting on the ventilator or off the ventilator, what other objective tests do you have as far as conditioning, performance status, physical condition? These are patients that many of them are ambulatory, have unilateral disease, and you are saying they feel better. Prove it.

Dr Raymond P. Onders: Data from the electromyograph. You can read the electrodes.

Dr Scott Melvin: That does not affect clinical behavior, though.

Dr Raymond P. Onders: It absolutely does. We have shown in our ALS trials that diaphragm electromyography correlates with diaphragm strength. It correlates with function of the diaphragm. We can now read the electrodes and differentiate muscle types. The size of the burst activity correlates with diaphragm strength, based on sleep studies, based on fluoroscopy. So early on, we were doing follow-up chest x-rays and fluoroscopy, but actually, once we were convinced with our other studies that we have shown that reading the implanted electrodes is probably all that we need to do for these patients.

Dr Scott Melvin: So how does that help somebody walk down the hallway? Can you show that they improved their performance? I mean, their x-ray looks better. I get that.
Dr Raymond P. Onders: Yes, and the subjective aspects, which we outlined further in the paper, actually, increased activity, shortness of breath. Because we did not have a formal study for that, I cannot say any more. That is one of the downfalls for it. A 6-minute walk test is what we do in lung transplantation. It is a good test to look for that, and that is probably what we would look at in a nonfunded study. We are trying to decrease patient costs. So that is just the way it was done.

Dr Frederick Rescorla (Indianapolis, IN): Does initial plication preclude or affect the success of later diaphragm pacing?

Dr Raymond P. Onders: Yes, it does. I kind of outlined that in the discussion, in discussing what to do for an elevated hemidiaphragm. If you have an acutely elevated hemidiaphragm, we have data that if you cut the phrenic nerve or something, that diaphragm will become paradoxically elevated significantly within 30 days.

The way you do a plication is you are going to actually crush the muscle and crush the nerve. And that prevents you from further diaphragm pacing, which the recommendations for diaphragm plication is you should wait ≥18 months before you plicate to see if it will recover on its own.

What we are looking at is whether or not, if you know you have an acute phrenic nerve injury, especially in lung transplant recipients, where you have to take the lung off, should you do the plication or should you just put the pacing wires in? We are now doing a prospective study in Europe, during lung transplantation, putting the wires in. So we can actually follow a problem.

That is actually going to be the way that we are going to address that in these high-risk patients in the intensive care unit is a prospective study. In Belgium, we are starting that trial. And we have just done a series of them in Switzerland also.

In 3 years, I'll present that here maybe.

Dr Ashraf Mansour (Grand Rapids, MI): If a patient in my institution needed a pacing procedure, could one of my partners do it or do we have to send them to Cleveland?

Dr Raymond P. Onders: That is a very good question. Diaphragm pacing for spinal cord injury and ALS are both under the FDA program for humanitarian device exemption, which means to implant those devices, even for spinal cord injury or ALS, you have to have an institutional review board protocol.

What we are doing is under a separate institutional review board protocol. It is an off-label use. It is only under institutional review board approval at this present time period.