Long-Term Follow-Up after Phrenic Nerve Reconstruction for Diaphragmatic Paralysis: A Review of 180 Patients

Matthew R. Kaufman, MD1,2  Andrew I. Elkwood, MD1  David Brown, MD3  John Cece, BS1  Catarina Martins, MA1  Thomas Bauer, MD4  Jason Weissler, MD5  Kameron Rezzadeh, MD2  Reza Jarrahy, MD2

1 Center for Treatment of Paralysis and Reconstructive Nerve Surgery, Jersey Shore University Medical Center, Neptune, New Jersey  
2 Division of Plastic and Reconstructive Surgery, David Geffen UCLA Medical Center, Los Angeles, California  
3 Department of Physical Medicine and Rehabilitation, JFK Medical Center, Edison, New Jersey  
4 Division of Thoracic Surgery, Jersey Shore University Medical Center, Neptune, New Jersey  
5 Department of Surgery, Robert Wood Johnson University Medical Center, New Brunswick, New Jersey

J Reconstr Microsurg

Abstract

Background  Phrenic nerve reconstruction has been evaluated as a method of restoring functional activity and may be an effective alternative to diaphragm plication. Longer follow-up and a larger cohort for analysis are necessary to confirm the efficacy of this procedure for diaphragmatic paralysis.

Methods  A total of 180 patients treated with phrenic nerve reconstruction for chronic diaphragmatic paralysis were followed for a median 2.7 years. Assessment parameters included: 36-Item Short Form Health Survey (SF-36) physical functioning survey, spirometry, chest fluoroscopy, electrodiagnostic evaluation, a five-item questionnaire to assess specific functional issues, and overall patient-reported outcome.

Results  Overall, 134 males and 46 females with an average age of 56 years (range: 10–79 years) were treated. Mean baseline percent predicted values for forced expiratory volume in 1 second, forced vital capacity, vital capacity, and total lung capacity, were 61, 63, 67, and 75%, respectively. The corresponding percent improvements in percent predicted values were: 11, 6, 9, and 13% (p ≤ 0.01; ≤ 0.01; ≤ 0.05; ≤ 0.01). Mean preoperative SF-36 physical functioning survey scores were 39%, and an improvement to 65% was demonstrated following surgery (p ≤ 0.0001). Nerve conduction latency, improved by an average 23% (p ≤ 0.005), and there was a corresponding 125% increase in diaphragm motor amplitude (p ≤ 0.0001). A total of 89% of patients reported an overall improvement in breathing function.

Conclusion  Long-term assessment of phrenic nerve reconstruction for diaphragmatic paralysis indicates functional correction and symptomatic relief.
Diaphragmatic paralysis is a respiratory disorder most commonly resulting from phrenic nerve dysfunction.\(^1\)\(^,\)\(^2\) Neural injury to the cervical roots, the phrenic nerve, or both, will reduce or eliminate conduction to the diaphragm muscle leading to hypotonia or atonia.\(^3\)\(^-\)\(^5\) Loss of diaphragmatic activity reduces passive lung expansion volumes leading to exertional dyspnea, orthopnea, sleep-disordered breathing, and a reduction in physical functioning.\(^3\)\(^,\)\(^4\) Although the long-term impact of diaphragmatic paralysis of the respiratory system has not been rigorously evaluated, it has been suggested that a chronic reduction in lower lung aeration not only compromises function, but also increases susceptibility to respiratory infections and the onset of obstructive pulmonary disorders.\(^5\)

The most common etiologies for diaphragmatic paralysis include an interscalene nerve block for rotator cuff surgery and cardiac surgery.\(^6\)\(^,\)\(^7\) Various interventions and procedures in the neck and chest have also been reported, such as: cervical lymphadenectomy, chiropractic manipulation, thoracic outlet surgery, thymectomy, cardiac ablation, and lobectomy.\(^8\)\(^,\)\(^9\) In many patients, without a clear traumatic or iatrogenic injury, there is a presumptive diagnosis of neuralgic amyotrophy (viral) or idiopathic neuropathy.\(^10\) Without an obvious etiology, appropriate evaluation should include radiographic imaging, not just of the neck and thoracic regions to rule out organic pathology, but also of the cervical spine to assess for cervical spondylosis and the possibility of a double-crush phenomenon.\(^11\)\(^,\)\(^12\)

Although plication of the diaphragm has been the surgical treatment option most familiar to clinicians, scattered case reports and a vast experience performing phrenic nerve reconstruction at our centers over the last 10 years has demonstrated it to be an effective alternative.\(^13\)\(^-\)\(^16\) Phrenic nerve reconstruction is specifically aimed at restoring diaphragmatic functional activity, something plication surgery does not achieve. Nerve reconstruction generally requires longer follow-up periods than static procedures due to the gradual neuromuscular recovery that occurs in accordance with the sequential processes of peripheral nerve regeneration and muscle strengthening.\(^17\)

The purpose of our study is to report long-term outcomes after phrenic nerve reconstruction for diaphragmatic paralysis.

### Methods

We performed an evaluation of 180 patients with unilateral diaphragmatic paralysis who underwent phrenic nerve reconstruction from September 2007 to December 2015. Of these 68 patients were previously reported in an earlier study.\(^14\) Patients were assessed and treated at two tertiary referral centers for multidisciplinary diaphragmatic paralysis management. Institutional review board approval at each institution was granted for the study and informed consent was obtained in accordance with study approval.

Diaphragmatic paralysis was confirmed using chest fluoroscopy (sniff testing) and quantified using pre- and intraoperative electrodiagnostics (nerve conduction studies [NCS] and electromyography [EMG]). Mean baseline percent predicted values were recorded for forced expiratory volume in 1 second (FEV\(_1\)), forced vital capacity (FVC), vital capacity (VC), and total lung capacity (TLC). Additional diagnostic testing included: computed tomography neck and chest to rule out mass lesions, and magnetic resonance imaging (MRI) cervical spine to evaluate for cervical spondylosis.

Cervical spondylosis with associated radiculopathy was diagnosed using both NCS/EMG testing and cervical spine MRI. All patients with positive findings were first referred for neurosurgical or spine surgeon assessment to determine whether there was an indication for cervical laminectomy.

Surgical treatment was pursued only after at least 8 months from onset without subjective or objective evidence of spontaneous improvement, except when there was a documented phrenic nerve transection injury. In the case of planned or inadvertent nerve sacrifice, surgery was offered promptly.

### Parameters for Assessment

#### Sniff Testing

Chest fluoroscopy was performed during the inspiratory and expiratory phases of breathing and used to diagnose paralysis of the diaphragm. Diaphragm elevation and absence of inspiratory motion, or paradoxical movement, was necessary to confirm the paralysis. The study was obtained or repeated within 3 months of surgical treatment, and reconfirmed in the operating room just before induction of anesthesia, and immediately after surgery to look for evidence of early change. Follow-up studies were performed within the first year and annually thereafter. Evidence of early improvement included a reversal of paradoxical movement, and/or a lower static diaphragmatic position with respect to the rib interspace. Optimal muscle recovery was demonstrated by the downward excursion of the diaphragm during inspiration.

#### Electrodiagnostic Evaluation

NCS of the phrenic nerve and EMG of the diaphragm were performed using standard methods. The ground electrode was placed on the upper sternum, the active surface electrode was placed over the lower sternum, and the reference electrode was placed 16 cm away over the anterior lower rib margin. The EMG was recorded using a 50-mm 26-gauge intramuscular monopolar needle electrode (Care Fusion, Middleton, WI) in the diaphragm and intercostal muscles. Ultrasound guidance was used to place the needle in the eighth or ninth intercostal space along the anterior axillary line. Each area was examined at rest and during volitional respiratory efforts. Patients were excluded from treatment if there were no identifiable voluntary motor units in the diaphragm.

#### Pulmonary Function Testing

Pulmonary spirometry was performed using standard techniques with patients sitting upright since most could not tolerate being supine. FVC, FEV\(_1\), VC, and TLC were measured (or calculated) and expressed as a percentage of the predicted values, in accordance with standard values based on patient age, height, and sex. Mean values for each spirometry parameter were determined preoperatively and following treatment.
SF-36 Survey
The 36-Item Short Form Health Survey (SF-36) consists of 36 questions assessing eight health concepts. The score for each health concept is directed into a 0 to 100 scale on the assumption that each question carries equal weight. A high score defines a more favorable health state. A physical function summary score was tabulated for each patient, and a mean score was determined for the treatment group.

Self-Reported Questionnaire of Specific Functional Issues
We asked patients five questions focused on symptoms commonly encountered with diaphragmatic paralysis, comparing presurgical findings with follow-up results to assist in reporting specific functional deficits and abilities. All patients initially provided negative responses to at least four out of five questions. Subjective improvement was recorded when the postoperative responses converted to positive for at least three questions. The questions were as follows:

1. Are you able to bend over and tie your shoes without feeling short of breath?
2. Are you able to lie flat in bed without feeling short of breath?
3. Are you able to run or walk up a flight of stairs without breathing difficulty?
4. Can you swim short distances in a pool without feeling short of breath?
5. Are you able to exercise at, or close to, the level of exertion before the onset of the diaphragmatic paralysis?

Patient-Reported Outcomes
As of most recent follow-up, patients were asked whether they are able to detect an overall improvement in respiratory function.

Statistical Analysis
Follow-up data were compared with baseline values using the Student t-test and a p value of less than or equal to 0.05 was considered significant.

Surgical Treatment
Phrenic Nerve Reconstruction
Phrenic nerve reconstruction was performed in the neck and/or chest using peripheral nerve surgery techniques detailed in prior publications. To summarize, the phrenic nerve was explored in the area of injury and decompressed via microsurgical neurolysis. Musculofascial and vascular adhesions were meticulously separated from the cervical roots and phrenic nerve. Sural nerve interposition grafting and/or neurotization (nerve transfer) from a nearby nerve donor were performed without functional sacrifice by using a redundant nerve branch or end-to-end grafting methods. Collagen nerve wraps (Axogen, Alachua, FL) were placed around both the phrenic nerve and nerve grafts to prevent recurrence of adhesions postoperatively. Thoracic approaches to phrenic nerve repair involved a combined effort by thoracic and reconstructive nerve surgeons for an approach to, and repair of the nerve defect. A video-assisted thoracoscopic (VATS) approach or minithoracotomy was used for intrathoracic access to the phrenic nerve for decompression and nerve grafting.

Surgical assessment included an analysis of operative times, length of hospital stay, and peri-/postoperative complications.

Results
There were 134 males and 46 females with an average age of 56 years (range: 10–79 years) and body mass index of 33.6 (range: 18.4–47.3) (Table 1). In 103 patients there was a right-sided paralysis, and left-sided paralysis was demonstrated in 77 patients. Adverse events during neck or chest surgery, invasive nonsurgical procedures, and cervical manipulation accounted for 49% of diaphragmatic paralysis, whereas 33% of cases resulted from trauma, and 13% were associated with cervical spondylosis. In the remaining 5% of diaphragmatic paralysis cases, there was no clear etiology. The average interval from onset to surgical treatment was 31 months (range: 5–120 months).

A cervical approach for phrenic nerve reconstruction was performed in 74% of patients, and 17% required a VATS or

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics and mean values of patients undergoing phrenic nerve reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td><strong>Values</strong></td>
</tr>
<tr>
<td>Age (y)</td>
<td>56</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>134</td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>33.6</td>
</tr>
<tr>
<td>Laterality (n)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>103</td>
</tr>
<tr>
<td>Left</td>
<td>77</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>49</td>
</tr>
<tr>
<td>Trauma</td>
<td>33</td>
</tr>
<tr>
<td>Spondylosis</td>
<td>13</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>5</td>
</tr>
<tr>
<td>Mean duration of paralysis (mo)</td>
<td>31</td>
</tr>
<tr>
<td>Surgical approach (%)</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>74</td>
</tr>
<tr>
<td>Thoracic</td>
<td>17</td>
</tr>
<tr>
<td>Combined</td>
<td>9</td>
</tr>
<tr>
<td>Mean operative time (h)</td>
<td>3.2</td>
</tr>
<tr>
<td>Mean length of stay (d)</td>
<td>1.3</td>
</tr>
<tr>
<td>Complications (%)</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2</td>
</tr>
<tr>
<td>Seroma</td>
<td>2</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>1</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.
A combined cervical and thoracic approach was required in 9% of patients. The mean operative time was 3.2 hours (range: 2–5.5 hours) and length of stay was 1.3 days (range: 1–4 days). Complications consisted of hematoma (2%), seroma (2%), pleural effusion (1%), and wound infection (1%). All patients were successfully extubated at the end of the procedure and there were no peri- or postoperative mortalities.

Mean baseline percent predicted values for FEV1, FVC, VC, and TLC were 61, 63, 67, and 75%, respectively. The corresponding postoperative values and percent improvement in percent predicted values were: 68, 67, 73, and 85%; and 11, 6, 9, and 13% ($p < 0.01$; $< 0.01$; $< 0.05$; $< 0.01$), respectively (►Fig. 1).

Mean preoperative SF-36 physical functioning survey scores were 39% (range: 0–100%) and improved to 65% following surgery ($p < 0.0001$) (►Fig. 2).

The average presurgical nerve conduction latency was 11.6 ms (reference: 7.0 ± 1.4 ms), and a 23% improvement (to 9.6 ms) was demonstrated following surgical treatment ($p < 0.005$) (►Fig. 3). There was a corresponding 125% increase in diaphragm motor amplitude (0.118–0.265 mV; reference: 0.75 ± 0.54 mV) ($p < 0.0001$) (►Fig. 4).

Preoperative chest fluoroscopy demonstrated complete paralysis of the diaphragm or paradoxical movement in all 180 patients. In 50% of patients, there was a reversal of paradoxical movement and an improved static position of the diaphragm the following treatment, whereas optimal fluoroscopic diaphragmatic activity (symmetrical static and dynamic positioning of the treated side when compared with the contralateral unaffected hemidiaphragm) was observed in 36% of patients.
The patient questionnaires indicated specific functional corrections (converting to positive responses in at least three of the five items) in 69% of patients. The highest conversion (92%) was observed for question 1, ability to bend over and tie one’s shoes without dyspnea, whereas the lowest conversion (65%) was reported for question 5, ability to exercise at preinjury levels without dyspnea. The conversion rates for questions 2 to 4 were: 76, 84, and 91%, respectively. In 89% of patients, there was a self-reported overall improvement in breathing function.

The median follow-up was 2.7 years (range: 6 months–9 years).

Discussion

The phrenic nerve provides sole innervation to the diaphragm, the most dominant muscle within the respiratory system. When the diaphragm contracts it shortens, flattens, and descends, permitting passive expansion of the lung. Unlike the intermittent activation of many other limb and trunk muscles throughout the body, there are constant demands on the diaphragm to maintain functional respiratory activity with each breath.

A loss of unilateral diaphragmatic function results in inefficient breathing due to ipsilateral inactivity of the lower lung, thereby reducing oxygen exchange. Although it is unusual for patients with this condition to be oxygen or ventilator dependent, the increased work of breathing commonly results in exertional dyspnea, orthopnea, and sleep-disordered breathing. Long-standing hypoinflation of the lower lung as a result of muscular paralysis may increase susceptibility to respiratory infection and the development of secondary obstructive lung disorders. A study by Khan et al evaluated the association between diaphragmatic dysfunction and sleep-disordered breathing, emphasizing the need for positive pressure ventilation for efficient sleep. Other case reports have elaborated on the susceptibility to recurrent lung infections in patients with hemidiaphragmatic paralysis.

Diaphragmatic paralysis reduces inspiratory effort resulting in a restrictive ventilatory defect primarily characterized on spirometry by a reduction in TLC, the total volume of air at full inhalation. When the TLC percent predicted value is below 80%, a restrictive defect is present. Additional findings typically include a reduction in FEV1, FVC, and VC, however, all of these values are obtained during an expiratory effort, despite the diaphragm being active only during inspiration. Accordingly, our analysis of patients undergoing phrenic nerve reconstruction found the greatest improvement in TLC, improving by 13% from a percent predicted value of 75 to 85%, a value that is well above the minimal threshold and within the normal range.

In addition to the profound impact of diaphragmatic paralysis on the respiratory system, there are secondary effects that have been associated with this neuromuscular disorder. For example, patients with left-sided diaphragmatic paralysis often present with gastroesophageal reflux, likely a result of the altered lower esophageal sphincter pressures with superior displacement of the lower esophagus and stomach. There is also evidence that inspiratory muscle dysfunction may be associated with low back pain due to the important role of the diaphragm in proprioceptive postural control.

Although cervical spondylosis has been associated with hemidiaphragmatic paralysis, the well-established double-crush phenomenon has not previously been applied to these patients. Our experience evaluating and treating numerous patients with this condition has uncovered a possible relationship between underlying cervical spondylosis and phrenic nerve injury. Although only 13% of our patients had cervical spondylosis as their primary etiology, many more did have mild-to-moderate cervical spine changes on MRI that may have worsened their primary iatrogenic or traumatic insult. Subsequent evaluations will most certainly explore this possibility further to enhance our understanding of the neuropathological processes that lead to this disorder.
The current outcomes analysis provides longer term follow-up of 180 patients, expanding on a prior study of 68 patients undergoing phrenic nerve reconstruction who were compared with a historical cohort that was treated with diaphragm plication.14 The most notable comparison between the two studies is the incremental improvement in diaphragm motor amplitude with longer follow-up. The average improvement in diaphragm motor amplitude after surgery increased from 37% at 1 year, to 125% after more than 2 years, strongly supporting the notion that muscle strengthening after peripheral nerve regeneration occurs incrementally, taking several years to reach optimal levels. Accordingly, we have coordinated an aggressive program of diaphragm retraining therapy with rehabilitation specialists to enhance muscle recovery after surgery.

Our multidisciplinary approach to patients with diaphragmatic paralysis includes multimodality therapy depending on the results of diagnostic workup (►Fig. 5). For example, patients are offered diaphragm plication surgery as a first-line therapeutic option versus phrenic nerve reconstruction if they fail to exhibit voluntary motor units on EMG testing, or are unable or unwilling to undergo aggressive postoperative diaphragm retraining therapy. Furthermore, we have recently begun to incorporate diaphragm pacemakers into the treatment plan simultaneous with phrenic nerve reconstruction for patients deemed “complex.” This would be applied to individuals presenting with remote injuries (> 10 years with intact motor units), bilateral diaphragmatic dysfunction, or hostile cervical or thoracic regions from radiation or extensive scarring. Implantation of diaphragm pacemakers for hemidiaphragmatic paralysis was first reported by Onders et al, who demonstrated an improvement in respiratory function in 62% of patients.26

**Conclusion**

Diaphragmatic paralysis is a neuromuscular disorder for which a functional surgical solution has previously been lacking. Recent investigation has supported the feasibility of phrenic nerve reconstruction. Our present study has clearly demonstrated efficacy and a functional alternative to diaphragm plication based upon the results of long-term follow-up in a large cohort of symptomatic patients.

### References


**Fig. 5** Multimodality treatment algorithm for diaphragmatic paralysis.