

Functional Restoration of Diaphragmatic Paralysis: An Evaluation of Phrenic Nerve Reconstruction

Matthew R. Kaufman, MD, Andrew I. Elkwood, MD, Alan R. Colicchio, MD, John CeCe, BS, Reza Jarrahy, MD, Lourens J. Willekes, MD, Michael I. Rose, MD, and David Brown, DO

Department of Surgery, Jersey Shore University Medical Center, Neptune, New Jersey; The Institute for Advanced Reconstruction, Shrewsbury, New Jersey; Department of Neuroscience, Jersey Shore University Medical Center, Neptune, New Jersey; Department of Surgery, Ronald Reagan UCLA Medical Center, Los Angeles, California; Department of Surgery, Riverview Medical Center, Red Bank, New Jersey; and Department of Physical Medicine and Rehabilitation, JFK Medical Center, Edison, New Jersey

Background. Unilateral diaphragmatic paralysis causes respiratory deficits and can occur after iatrogenic or traumatic phrenic nerve injury in the neck or chest. Patients are evaluated using spirometry and imaging studies; however, phrenic nerve conduction studies and electromyography are not widely available or considered; thus, the degree of dysfunction is often unknown. Treatment has been limited to diaphragmatic plication. Phrenic nerve operations to restore diaphragmatic function may broaden therapeutic options.

Methods. An interventional study of 92 patients with symptomatic diaphragmatic paralysis assigned 68 (based on their clinical condition) to phrenic nerve surgical intervention (PS), 24 to nonsurgical (NS) care, and evaluated a third group of 68 patients (derived from literature review) treated with diaphragmatic plication (DP). Variables for assessment included spirometry, the Short-Form 36-Item survey, electrodiagnostics, and complications.

Results. In the PS group, there was an average 13% improvement in forced expiratory volume in 1 second ($p < 0.0001$) and 14% improvement in forced vital capacity

($p < 0.0001$), and there was corresponding 17% ($p < 0.0001$) and 16% ($p < 0.0001$) improvement in the DP cohort. In the PS and DP groups, the average postoperative values were 71% for forced expiratory volume in 1 second and 73% for forced vital capacity. The PS group demonstrated an average 28% ($p < 0.01$) improvement in Short-Form 36-Item survey reporting. Electrodiagnostic testing in the PS group revealed a mean 69% ($p < 0.05$) improvement in conduction latency and a 37% ($p < 0.0001$) increase in motor amplitude. In the NS group, there was no significant change in Short-Form 36-Item survey or spirometry values.

Conclusions. Phrenic nerve operations for functional restoration of the paralyzed diaphragm should be part of the standard treatment algorithm in the management of symptomatic patients with this condition. Assessment of neuromuscular dysfunction can aid in determining the most effective therapy.

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The symptomatology associated with unilateral diaphragmatic paralysis includes exertional dyspnea, orthopnea, sleep disturbances, and gastrointestinal reflux [1–3]. The loss of diaphragmatic tone alters the pressure differential between the thoracic and abdominal compartments, thus reducing the thoracic volume and permitting the abdominal contents to migrate superiorly [4]. Absence of diaphragmatic contraction reduces expansion of the lung during inspiration, resulting in a restrictive ventilatory deficit [5].

Although the consequence of this condition primarily affects the respiratory system, the underlying pathophysiology is neuromuscularly derived. Diagnostic evaluations commonly performed to confirm diaphragmatic paralysis include sniff testing (chest fluoroscopy performed during inspiration), computed tomography/

magnetic resonance imaging, and spirometry. Electrodiagnostic testing by a nerve conduction study (NCS) or electromyography (EMG) is not, however, routine, perhaps due to a lack of widespread availability.

The primary purpose of NCS/EMG testing for diaphragmatic paralysis, or for any peripheral nerve injury, is to evaluate nerve conduction and assess motor unit potentials [6]. As long as motor unit potentials are present, the possibility exists to restore muscle function in the event of reinnervation. Standard principles of peripheral nerve injury treatment clearly distinguish the indications for functional nerve repair (when the possibility of reinnervation exists) from static procedures (when motor unit potentials are undetectable) [7].

Until recently, plication of the diaphragm has been the only available treatment option for paralysis. However, the degree of neuromuscular dysfunction has not been reported in outcome studies evaluating this procedure [8–12]. Functional restoration of a paralyzed diaphragm (or of any skeletal muscle) by correcting or reversing the underlying neuropathy would be the ideal initial therapy

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Address correspondence to Dr Kaufman, The Institute for Advanced Reconstruction, 535 Sycamore Ave, Shrewsbury, NJ 07702; e-mail: kaufmanmatthew@hotmail.com.

when spontaneous improvement does not occur. The purpose of our study was to assess outcomes of phrenic nerve surgical intervention (PS), nonsurgical care (NS), and diaphragmatic plication (DP) in symptomatic patients with hemidiaphragmatic paralysis. We propose that PS be added to an expanded treatment algorithm (Fig 1) that also retains DP as an option.

Patients and Methods

The Jersey Shore University Medical Center (Neptune, NJ) Institutional Review Board approved the study, and informed patient consent was obtained in accordance with study approval.

Patient Population

Our interventional study evaluated 92 consecutive patients with symptomatic hemidiaphragmatic paralysis between January 2008 and December 2012 at our tertiary referral center. On the basis of their clinical condition, the 92 patients were offered PS or were evaluated as part of the nonsurgical group (NS). Our tertiary referral center provides comprehensive care to patients with diaphragmatic paralysis that includes PS and DP. Because our recruitment area comprises the entire United States and patients seeking treatment often travel a distance to our center, those who were offered DP generally chose to seek treatment closer to home because it was readily available in their geographic area. Thus, most were lost to follow-up, and we were not able to accumulate a matching DP cohort.

Treatment Groups

PS GROUP. The patients who qualified for PS (n = 68) had to exhibit symptomatic hemidiaphragmatic paralysis,

without interval improvement on NCS/EMG and sniff testing, for a minimum of 8 months. The NCS/EMG study had to demonstrate a reduction in conduction latency and motor amplitude compared with the uninvolved side. The sniff test had to reveal absence of diaphragmatic motion or paradoxical motion but normal activity in the contralateral hemidiaphragm.

NS GROUP. Twenty-four patients were enrolled in the NS group. Allocation to the NS group was based on absence of traumatic or iatrogenic injury or when there was high suspicion of a viral neuritis (ie, flu-like symptoms, upper extremity pain/weakness). In patients who did report a history of iatrogenic injury or trauma, enrollment in the NS group occurred if there was evidence of spontaneous clinical improvement, if an alternative etiology was elicited on diagnostic evaluation (ie, systemic disease), or if the EMG revealed absence of motor unit potentials. These patients had refused DP or were poor surgical candidates.

DP GROUP. A structured protocol was used to compile the historical cohort of patients who underwent DP (Fig 2) [13]. The study review included assessment of study type, number of patients, surgical approach, spirometry values, dyspnea score, complications, and deaths. Criteria for DP group ineligibility were case report or small series (<10 patients), follow-up of less than 12 months, duplication of study population by other included reports, or more than 12 years from the publication date. We included only studies that presented mean data for pretreatment and posttreatment spirometry (forced expiratory volume in 1 second [FEV₁] and forced vital capacity [FVC]), complications, and deaths. Systematic review resulted in four studies comprising 68 patients available for outcome analysis [8-11]. Risk of bias in individual studies (and

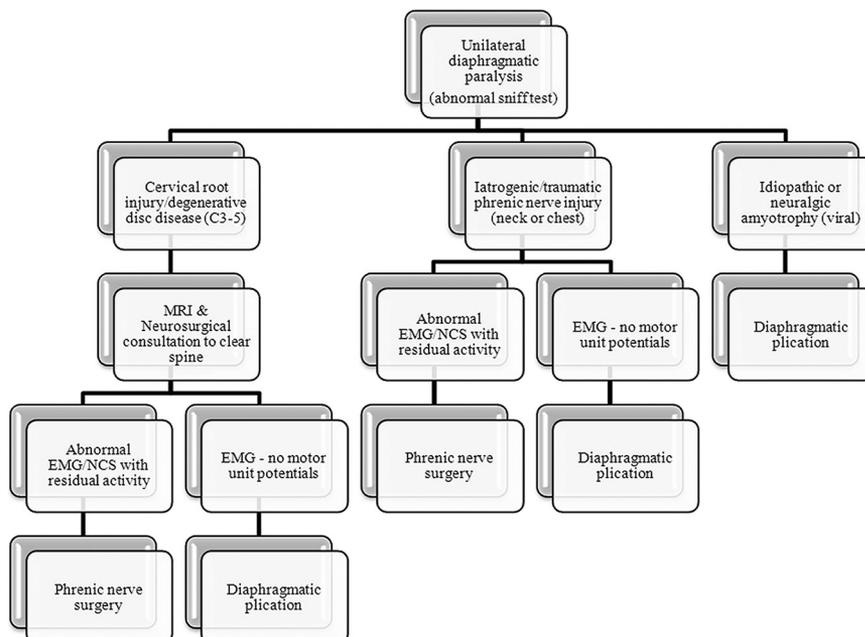
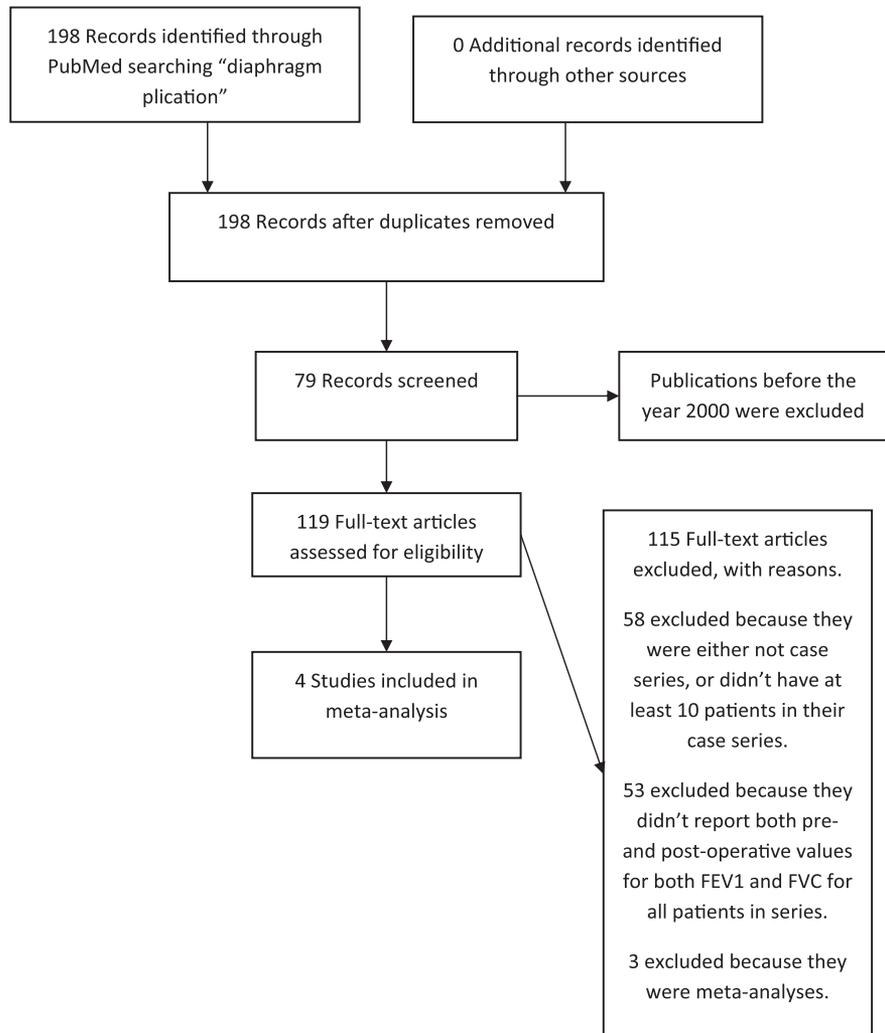


Fig 1. Treatment algorithm for management of symptomatic diaphragmatic paralysis. (EMG = electromyography; MRI = magnetic resonance imaging; NCS = nerve conduction study.)

Fig 2. Flow diagram shows construction of the meta-analysis. (FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.)



across studies) was evaluated by study design and comprehensiveness of data reporting.

Diagnostic Tests

Diagnostic evaluation included: sniff testing, CT/MRI, spirometry, NCS/EMG, blood work, and the Medical Outcomes Study Short-Form 36-Item (SF-36) survey.

PULMONARY FUNCTION TESTS. Pulmonary spirometry was performed with the patients upright because most patients could not tolerate being supine. Preoperative and follow-up FVC and FEV₁ were measured and expressed as a percentage of the predicted values. Comparative assessments were performed on the percentage change of the percentage predicted value.

ELECTRODIAGNOSTIC EVALUATION. 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. Baseline electrodiagnostic evaluations were undertaken in all patients in the PS and NS groups. Each area was examined at rest and during volitional respiratory efforts.

SF-36 SURVEY. The SF-36 consists of 36 questions assessing eight health concepts [14]. 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 each treatment group.

Surgical Treatment

PS, detailed in our earlier report [15], includes nerve decompression, interposition nerve grafting for segmental phrenic nerve injury, and nerve transfer for a proximal phrenic nerve or a cervical root lesion. Phrenic

Table 1. Baseline Data in the Three Groups With Diaphragmatic Paralysis

Group	No.	Age (y)	Sex, No.		Side			BMI (kg/m ²)	Amp (mV)	NCS (msec)	F/U (mos)
			M	F	Right	Left	BL				
PS	68	53	53	15	28	40	0	30.2	0.24	10.9	12
NS	24	62	22	2	10	11	2	28.4	0.23	11.6	22
DP ^a	68	58	42	26	21	47	0	NR	NR	NR	64

^a Higgs (2002) [8], Mouroux (2005) [9], Groth (2010) [10], Celik (2012) [11].

BL = bilateral; BMI = body mass index; DP = diaphragmatic plication; F = female; F/U = follow-up; M = male; NCS = nerve conduction study; NR = not reported; NS = nonsurgical; PS = phrenic nerve surgical procedure.

nerve decompression consists of removing fascial, vascular, and muscular sites of adherence. Nerve grafting involves bypassing an abnormal segment or segments of phrenic nerve using a harvested nerve donor. Nerve transfer reroutes a nearby functioning nerve into the phrenic nerve to promote regeneration.

Statistical Analysis

Follow-up data were compared with baseline values using the Student *t* test for paired and unpaired data, when appropriate. The Pearson correlation coefficient (*r*) was calculated for baseline and follow-up spirometry, electrodiagnostics, and SF-36. For all tests, a two-sided *p* value of less than 0.05 was considered significant.

Results

PS Group

The PS group comprised 53 male and 15 female patients, with an average age of 53 years (range, 11 to 79 years) and a mean body mass index of 30.2 ± 5.3 kg/m² (Table 1). The paralysis was left-sided in 40 patients and right-sided in 28. All patients provided a history of an episodic or recurrent iatrogenic or traumatic event or events (Table 2). The average duration between onset of respiratory symptoms and surgical treatment was 22 months (range, 8 to 72 months). The follow-up period after treatment averaged 12 months (range, 6 to 61 months).

Fifty-two patients underwent a cervical approach to the phrenic nerve for decompression and nerve grafting, and 16 patients underwent a lateral thoracotomy to access the nerve in the mediastinum or chest cavity, or both. There were no perioperative or postoperative deaths and no cases of pneumonia or respiratory failure. Complications were hematoma (3%), localized infection at the nerve graft harvest site (3%), and pleural effusion (1%).

NS Group

There were 2 female and 22 male patients, with an average age of 62 years (range, 41 to 88 years) and a mean body mass index of 28.4 ± 10.8 kg/m² (Table 1). The paralysis was right-sided in 10 patients, left-sided in 11, and bilateral in the remaining 3. The suspected etiology was viral or idiopathic in 14 patients. The remaining 10 patients reported a preceding iatrogenic or traumatic injury, but they were not offered surgical intervention because of

exclusion criteria. The average follow-up period was 22 months (range, 7 to 60 months).

DP Group

The four case series deemed suitable for cohort analysis consisted of 69 patients, with follow-up data for assessment in 68 patients (1 patient died of postoperative sepsis and was excluded; Table 1). There were 42 male and 26 female patients, with an average age of 58 years (range, 24 to 73 years). In the DP group, 32 thoracotomies were performed and 36 minimally invasive procedures, consisting of video-assisted thoracoscopic surgery in 12 and laparoscopic in 24. The average patient follow-up was 64 months. Diaphragm paralysis was right-sided in 21 patients and left-sided in 47. Comparative analysis of preoperative and postoperative (Medical Research Council/American Thoracic Society) dyspnea scores was performed in 31 patients, revealing an average improvement of 1.6 points. SF-36 scores were not reported in the four collated DP studies. The complication rate was 15%, and surgical mortality was 1%.

Pulmonary Spirometry Follow-Up

The mean baseline values for FEV₁ in the PS, NS, and DP groups were $63\% \pm 14\%$, $64\% \pm 21\%$, and $60\% \pm 5\%$, respectively. The average improvements in FEV₁ after treatment in the PS and DP groups were $13\% \pm 11$ ($p < 0.0001$) and $17\% \pm 7$ ($p < 0.0001$), respectively (Fig 3). In the NS group, the average interval change in FEV₁ was $1.7\% \pm 6\%$ ($p = 0.25$). The corresponding baseline FVC

Table 2. Suspected Etiology of Diaphragmatic Paralysis in the Group Undergoing Phrenic Nerve Surgical Procedures

Suspected Etiology	No. (%)
Nerve block (interscalene/epidural)	18 (27)
Neck/spine trauma	16 (24)
Cardiac operation	11 (16)
Neck operation (thyroid, lymphadenectomy)	5 (7)
Chiropractic	5 (7)
Thymectomy	3 (4)
Radiofrequency ablation (cardiac)	3 (4)
Thoracic outlet operation	3 (4)
Carotid-subclavian bypass	2 (3)
Pulmonary lobectomy	2 (3)
Total	68 (100)

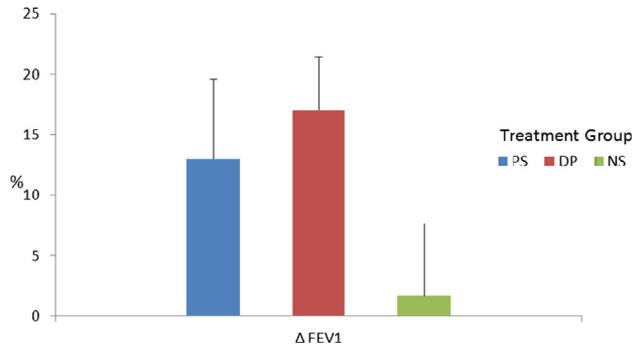


Fig 3. Average change in forced expiratory volume in 1 second (FEV₁, %) in patients undergoing phrenic nerve surgical procedures (PS), diaphragmatic plication (DP), or those managed nonsurgically (NS).

values in the PS, NS, and DP groups were 65% ± 14%, 67% ± 15%, and 63% ± 6%, respectively. FVC improved by an average of 14% ± 12% ($p < 0.0001$) in the PS group and 17% ± 14% ($p < 0.0001$) in the DP group, whereas in the NS group, there was an average -0.4% ± 4% ($p = 0.4$) change in FVC (Fig 4). There was a nonstatistical trend toward enhanced percentage improvement for FEV₁ in the DP group compared with the PS group (17% ± 7% vs 13% ± 11%; $p = 0.08$), and a corresponding significant difference for FVC (17% ± 14 vs 14% ± 12%; $p < 0.05$), respectively. The percentage changes in FEV₁ and FVC from baseline were significantly greater in the PS and DP groups than in the NS group (FEV₁: 13% ± 11% vs 1.7% ± 6% [$p < 0.05$]; 17% ± 7% vs 1.7% ± 6% [$p < 0.001$]; and FVC: 14% ± 12% vs -0.4% ± 4% [$p < 0.01$]; 17% ± 14% vs -0.4% ± 4% [$p < 0.001$], respectively). The average postoperative values were 71% for FEV₁ and 73% for FVC in the PS and DP groups.

Electrodiagnostic Follow-Up

The mean baseline values for nerve conduction latency were 10.9 ± 4.1 msec in the PS group and 11.6 ± 4.4 msec NS group (reference, 7 ± 1.4 msec; Table 1). The corresponding mean values for motor amplitude were 0.24 ± 0.17 mV in the PS group and 0.23 ± 0.15 mV in the NS group (reference, 0.75 ± 0.54 mV). Comparative

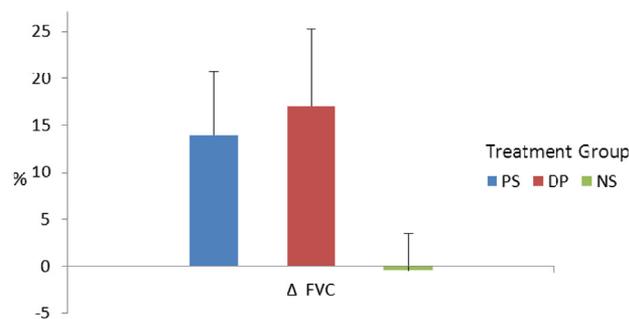


Fig 4. Average change in forced vital capacity (FVC, %) in patients undergoing phrenic nerve surgical procedures (PS), diaphragmatic plication (DP), or those managed nonsurgically (NS).

analysis between preoperative and postoperative electrodiagnostic testing results in the PS group revealed an average improvement of 69% in nerve conduction latency ($p = 0.036$) and 37% in motor amplitude ($p < 0.0001$).

Sf-36 Follow-Up

The preoperative SF-36 average result in the PS group was 41% ± 21% (normal, 100%), and a mean improvement of 28% ± 20% ($p = 0.004$) was demonstrated after PS (Fig 5). The corresponding baseline SF-36 result in the NS group was 54% ± 18%, and an average change of 4% ± 8% ($p = 0.16$) was calculated during follow-up analysis.

Sniff Test Follow-Up

Comparative analysis of preoperative and postoperative sniff test results in the PS group revealed an unequivocal reversal of paradoxical motion and evidence of functional movement in 80% of those whose baseline examinations exhibited one or both of these abnormalities. In the remaining 20%, the postoperative examinations demonstrated a reversal of paradoxical motion (when previously exhibited) without demonstrable functional activity or no clearly discernible improvement (when paradoxical motion was not seen on baseline study).

Comment

Diaphragmatic paralysis is a disorder that is not readily recognized, primarily because it is unlike many other respiratory diseases in which the underlying pathophysiology affects the airways or lung parenchyma, or both. Respiratory deficits caused by dysfunction of the primary respiratory muscle are most often a direct result of injury to its innervation, the phrenic nerve. The etiology can be iatrogenic injury (ie, surgical, anesthetic blocks, chiropractic) or trauma (ie, whiplash, traction injury). If no obvious event occurred concomitant with the onset of respiratory symptoms, inquiries about chronic, repetitive trauma are necessary. For example, a patient had been

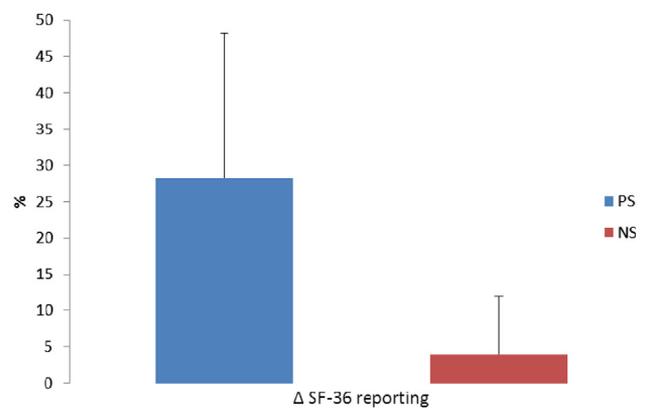


Fig 5. Average change in Short-Form 36-Item (SF-36) survey reporting from baseline is shown in the groups undergoing phrenic nerve surgical procedures (PS) and nonsurgical (NS) treatment. (Note: The studies comprising the plication analysis did not report SF-36 results).

lifting heavy wood beams across his neck and shoulder every day for several weeks, and respiratory symptoms developed that were conclusively a result of a newly paralyzed diaphragm. Intraoperative findings in this patient were consistent with a severe compression neuropathy of the phrenic nerve. There are many examples of this clinical scenario as the underlying etiology for peripheral nerve injuries occurring in the upper and lower extremities [16].

Repetitive injury and trauma to a nerve may result in microvascular (ischemic) changes, edema, injury to the outside layers of the nerve (myelin sheath) that aid in the transmission of the nerve's messages, and structural alterations in membranes at the organelle levels in both the myelin sheath and the nerve axon. Focal segmental demyelination at the area of compression is a common feature of compression syndromes. Complete recovery of function after surgical decompression reflects remyelination of the injured nerve. Incomplete recovery in more chronic and severe cases of entrapment is due to Wallerian degeneration of the axons and permanent fibrotic changes in the neuromuscular junction that may prevent full reinnervation and restoration of function [17].

Although diaphragmatic paralysis can be confirmed rather simply with a sniff test, none of the currently available radiographic examinations can accurately diagnose a phrenic nerve injury. The caliber of the nerves of the brachial plexus allows for detailed visualization on magnetic resonance neurography, thus permitting diagnosis of structural injury using this modality; however, the smaller diameter of the phrenic nerve prohibits accurate evaluation by current standards [18]. Because of the lack of an adequate radiographic test, NCS/EMG is necessary to confirm and quantify phrenic injury.

If a response can be recorded from a transmitted impulse along the phrenic nerve, it demonstrates nerve continuity and the likelihood that motor end plates will be maintained. The confirmation of motor end-plate viability is through demonstration of motor unit potentials on EMG. These electrodiagnostic findings in a patient providing a history of iatrogenic or traumatic injury, without any clinical or radiographic improvement after 8 months, clearly confirm an indication for operative nerve repair (Fig 1). Alternatively, if the EMG fails to demonstrate motor unit potentials and there is an absence of a transmitted impulse on NCS, then nerve repair is likely futile and the patient would be better served with a static procedure.

Current treatment standards use this algorithmic approach for virtually all other peripheral nerve injuries [19]. The most striking analogy is in the case of a peroneal nerve injury causing a foot-drop. Treatment options consist of peroneal nerve repair, muscle transfer, or ankle fusion. Performing an ankle fusion in a patient with an incomplete peroneal nerve injury would be unthinkable even though the functional outcomes associated with ankle fusion are favorable [20]. Medical standard of care is peroneal nerve repair [21]. Implicit in this methodology is retaining the possibility of ankle fusion as a salvage procedure in the event of an unsuccessful nerve repair.

The algorithmic approach outlined in this study is based on demonstrated favorable outcomes after phrenic nerve operations and plication of the diaphragm, and the notion that whereas the phrenic nerve operation does not exclude the possibility for subsequent plication, a failed plication procedure cannot likely be salvaged with diaphragmatic reinnervation due to intramuscular scarring and fibrosis. The proposed algorithm and study design are characterized by an emphasis on multimodality (PS and DP both as options) rather than exclusionary management (PS vs DP) of diaphragmatic paralysis to maximize the likelihood of short-term or long-term recovery.

The outcomes of our study demonstrate a significant improvement in respiratory activity in the DP and PS groups. Comparison between the preoperative and postoperative mean percentage of predicted values for FEV₁ and FVC after treatment in the DP and PS groups revealed a categorical upgrade from moderate flow reductions (60% to 69% of predicted) to mild flow reductions (70% to 79% of predicted). Analysis showed a nonstatistical trend toward enhanced percentage improvement in percentage predicted values in the DP group compared with the PS group for FEV₁ and a statistically significant difference for FVC. These findings may indicate that plication leads to slightly better improvements in respiratory function than the phrenic nerve operation, or alternatively, that the phrenic nerve operation may result in a more gradual improvement in respiratory function compared with plication.

Thus, it is possible that longer follow-up assessments (beyond a mean of 12 months) may reveal progressive functional corrections. This notion is supported by the electrodiagnostic outcomes revealing improvements of 69% in nerve conduction latency and 37% in motor amplitude. Previous prospective studies have demonstrated the value of electrodiagnostic testing for prognosticating clinical recovery [22] and determining whether a lack of early clinical improvement indicates failed nerve regeneration and a need for a secondary operation [23]. The 7% complication rate and 0% mortality in the PS group compare favorably with a 15% complication rate and 1% surgical mortality in the DP group.

Assessment of recovery after nerve reconstruction has to be undertaken for a period of at least 1 year or longer for accurate reporting. Although early recovery will sometimes occur from nerve decompression alone, nerve regeneration (after grafting) occurs at a rate of 1-mm/d from the injury location to the target muscle [24]. The reinnervated muscle must then be rehabilitated to restore force and function to segments that have undergone atrophy. The literature is replete with examples of long-distance peripheral nerve regeneration occurring in the extremities and face, at rates of 80% or higher [25–27]. In our series we have observed improvements in diaphragmatic function through patient reporting and diagnostic evaluations occurring even 2 to 3 years after treatment. We suspect this is due to ongoing muscle reactivation and strengthening and has been most notable in patients engaging in a formal program of

pulmonary rehabilitation or a self-driven exercise regimen.

Muscle reinnervation will rarely, if ever, restore 100% of normal muscle function, especially in an older injury denervation that has been ongoing [28]. However, our results strongly suggest a benefit in respiratory and physical function that can be demonstrated with partial muscle recovery as determined by electrodiagnostic testing. We suspect that with partial functional return, it is possible to reverse preexisting paradoxical motion, improve static force, and in many patients, initiate downward motion with inspiration. Although the sniff test results may still indicate diminished movement when compared with the normally functioning side, the capacity for lung volume expansion clearly improves, as determined by postoperative spirometry. Longer follow-up will confirm whether ongoing muscle recovery leads to progressive inspiratory improvements in diaphragmatic excursion and lung function.

We have demonstrated a benefit of phrenic nerve operations in the management of unilateral diaphragmatic paralysis that is comparable to plication and superior to nonsurgical management. Although there are study limitations (ie, nonrandomized, PS follow-up of only 12 months, DP group is a historical cohort), the favorable outcomes support an expanded treatment algorithm using electrodiagnostics to classify the phrenic nerve injury. Thus, patients with diaphragmatic paralysis could be offered the more appropriate of two effective surgical options to improve respiratory activity.

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INVITED COMMENTARY

The article from Kaufman and colleagues [1] provides the strongest evidence to date in favor of a sea-change in how one might approach patients with diaphragmatic

paralysis. Whereas the current treatment paradigm dictates diaphragm plication (now generally done by video-assisted thoracic surgery) in symptomatic patients with a