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Original Research

CARDIOTHORACIC SURGERY

Reinnervation of the Paralyzed Diaphragm

Application of Nerve Surgery Techniques Following Unilateral Phrenic Nerve Injury

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Background: **Unilateral phrenic nerve injury often results in symptomatic hemidiaphragm paralysis, and currently few treatment options exist. Reported etiologies include cardiac surgery, neck surgery, chiropractic manipulation, and interscalene nerve blocks. Although diaphragmatic plication has been an option for treatment, the ideal treatment would be restoration of function to the paralyzed hemidiaphragm. The application of peripheral nerve surgery techniques for phrenic nerve injuries has not been adequately evaluated.**

Methods: **Twelve patients presenting with long-term, symptomatic, unilateral phrenic nerve injuries following surgery, chiropractic manipulation, trauma, or anesthetic blocks underwent a comprehensive evaluation, including radiographic and electrophysiologic assessments. Surgical treatment was offered following a minimum of 6 months of conservative management. Operative planning was based on preoperative and intraoperative testing using one or more established nerve reconstruction techniques (neurolysis, interpositional grafting, or neurotization).**

Results: **Measures of postoperative improvement included pulmonary function testing, fluoroscopic sniff testing, and a standardized quality-of-life survey, from which it was determined that eight of nine patients who could be completely evaluated experienced improvements in diaphragmatic function.**

Conclusions: **Based on the favorable results in this small series, we suggest expanding nerve reconstruction techniques to phrenic nerve injury treatment and propose an algorithm for treatment of unilateral phrenic nerve injury that may expand the current limitations in therapy.**

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Abbreviations: EMG = electromyography; MUP = motor unit potential; NCS = nerve conduction study; PFT = pulmonary function test; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey

One of the most devastating sequelae of cardiac surgery today is phrenic nerve injury: Bilateral injury may lead to ventilator dependence, whereas unilateral injury may decrease pulmonary function, resulting in an overall reduction in physical capacity.[1-5] Other causes of phrenic nerve injury may include interscalene or epidural nerve blocks, neck or mediastinal surgery, chiropractic manipulation, and trauma.[6-9]

Currently, operative management in adults has not been studied extensively; the only procedure being performed with any regularity is diaphragmatic plication.[10,11] Furthermore, although it may work for the

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pediatric population, the benefits of diaphragmatic plication in the adult population have yet to be clearly elucidated. Diaphragmatic pacemakers, though proven successful in cases of bilateral phrenic nerve injury, are not commonplace for unilateral injury because of the inability of the pacemaker to synchronize with spontaneous respiratory drive. Phrenic nerve grafting for acutely injured nerves has been shown to be effective in rare cases.[12,13]

Whereas neurolysis, nerve grafting, and neurotization are common surgical techniques in the treatment of brachial plexus injuries and paralysis of the upper and lower extremities, their application for injuries to the phrenic nerve have been reported only in isolated cases of acute injury.[12,13] Neurolysis is the surgical release of inflammatory adhesions that typically is performed with magnification in order to free the nerve from sites of tension or compression. Nerve grafting and neurotization (aka, nerve transfer) are techniques performed when the nerve injury is more complete. For example, if neurolysis alone will not reverse the deficit, either an interposition nerve graft to bypass the site of injury or a nerve transfer to provide an alternate source of impulse, may be necessary to restore function to the innervated muscle. Here, we present 12 cases of diaphragm reinnervation following unilateral phrenic nerve injury and propose an algorithm for treatment of these often-debilitating injuries previously thought to be irreversible.

The Bottom Line

How does this work advance the field?

To date, few treatment options exist for patients with diaphragm paralysis and only rarely, in case reports, has diaphragm reinnervation been documented in the literature. This study demonstrates that it may be possible for nerve surgery to restore function to a paralyzed diaphragm, representing an innovation with the potential to advance the fields of pulmonary medicine and surgery.

What are the clinical implications?

Many patients experience unresolved diaphragm paralysis, mostly from surgical or anesthetic injuries, and very few can be treated. Diaphragm plication can help some patients, but the present study details a therapeutic option that may actually restore function to the diaphragm itself and provide a more physiologic functional improvement to many patients.

Materials and Methods

We retrospectively reviewed 12 patients presenting with hemidiaphragm paralysis refractory to conservative therapy who underwent surgical treatment between September 2007 and September 2010. This group of patients was selected from a much larger cohort of patients who were evaluated but found not to be candidates for therapy. The institutional review board at our hospital approved the study, and informed consent was obtained in accordance with study approval.

The algorithm for treatment of these injuries was based on information gathered from clinical history, pulmonary function tests (PFTs), nerve conduction study (NCS), electromyography (EMG), and radiographic imaging. Patients were excluded from treatment if there was any clinical evidence of spontaneous interval improvement in function or if NCS/EMG testing was normal. Patients with normal preoperative PFTs were not excluded from treatment if other abnormalities were present. All PFTs were performed in the seated position because of patient difficulties in tolerating supine evaluation; therefore, resultant values may not have completely captured the extent of the restrictive functional deficit. Restrictive ventilatory deficits associated with unilateral diaphragm paralysis are exacerbated in the supine position. The increased intraabdominal hydrostatic pressure is unopposed by the flaccid hemidiaphragm, resulting in a loss of thoracic domain.

In order to qualify for treatment, patients had to exhibit diaphragm paralysis and abnormalities on NCS/EMG testing for at least 6 months. This criterion is based on published data indicating that patients with a range of peripheral nerve injuries who fail to exhibit clinical or electrophysiologic evidence of improvement over a 6-month period have a rather remote likelihood of spontaneous improvement and that surgical success rates will be reduced if repair is delayed beyond this time frame when there is a complete nerve transection injury.[14]

The evoked NCS of the phrenic nerve was performed by stimulation at the junction of the mid and distal third of the posterolateral margin of the sternocleidomastoid muscle. The ground electrode was placed on the anterior-superior iliac crest. The active electrodes were placed over both the eighth and the ninth intercostal spaces. The EMG was performed using a 50-mm, 25-gauge intramuscular monopolar needle electrode in the diaphragm and external and internal intercostal muscles. Each area was examined during needle insertion at rest and with attempted volitional respiratory activity.

The algorithm we followed and are proposing for treatment of unilateral phrenic nerve paralysis is as follows: (1) Patients are not offered surgery (or offered diaphragm plication) if the etiology of the injury cannot be clearly elucidated or if NCS/EMG testing demonstrates complete degeneration and muscle atrophy; (2) nerve exploration and neurolysis are performed at the site of injury when information gathered suggests an irreversible nerve injury with intact motor unit potentials (MUPs) on NCS/EMG testing; and (3) nerve exploration, neurolysis, and interpositional grafting (or neurotization) in the neck and chest are performed simultaneously when there is a complete denervation injury or root-level injury with intact MUPs or when there is an incomplete injury that cannot be reversed with neurolysis alone. Patients were evaluated with intraoperative NCS/EMG both before and after neurolysis. When comparative intraoperative testing failed to demonstrate improvement, immediate nerve grafting or neurotization was performed.

Parameters for outcome evaluation were etiology of injury, duration between injury and treatment, treatment offered, time from surgery to clinical response, PFTs, fluoroscopic sniff testing, and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (e-Appendix 1).[15] Postoperative evaluations were performed within the first 3 months in patients who underwent neurolysis alone or in nerve graft/nerve transfer patients who reported subjective respiratory improvement. For the remaining patients, testing was performed at approximately 1 year following surgical treatment. Outcomes were judged successful if sniff test reports, read by radiologists blinded to the treatment, demonstrated a reversal of either complete paralysis or paradoxical diaphragm movement on sniff testing in association with enhanced quality-of-life assessment reporting and increases in FEV_1 and FVC.

Results

There were eight men and four women with an average age of 54 years (range, 40-68 years). Paralysis followed anesthetic blocks in two patients (cervical epidural block [n = 1] and interscalene block [n = 1]) and followed surgical procedures in six (coronary artery bypass graft [n = 1], neck dissection for thyroid cancer [n = 2], carotid-subclavian bypass [n = 2], and cervical rib resection for thoracic outlet syndrome [n = 1]). The etiology for the remaining four patients was most likely cervical chiropractic manipulation (n = 2) and a traumatic event (n = 2) determined based on the correlation between onset of paralysis and timing of occurrences (Table 1).

Diaphragm paralysis was left sided in nine patients and right sided in three. Patients, by study design, had abnormally low or absent compound motor action potentials on NCS and demonstrated intact, but abnormal MUPs on EMG. Five of the patients evaluated demonstrated a complete conduction block, whereas partial denervation was seen on the NCS of the remaining seven patients. All 12 patients demonstrated either absence of motion or paradoxical diaphragm movement on preoperative sniff testing. Eight patients exhibited PFT parameters consistent with a restrictive abnormality, as characterized by a reduction in FVC without a reduction in FEV_1/FVC, whereas four patients with symptomatic diaphragm paralysis had normal values on preoperative PFTs. Four patients had additional associated neuropathies identified clinically and on NCS/EMG testing (spinal accessory [n = 1], long thoracic nerve [n = 1], ulnar nerve [n = 2]).

The average duration between onset of paralysis and surgical treatment was 30 months (range, 8-64 months). In all 12 patients, the phrenic nerve was identified and a neurolysis performed; seven patients also had an identifiable accessory phrenic nerve that was treated in the same manner. A sural nerve interposition graft was performed in seven patients, four of whom required both a cervical approach and a thoracotomy to access the phrenic nerve and bypass the site of injury, whereas in the remaining three, the interposition graft was performed completely in the neck. Two patients underwent an end-to-side neurotization procedure based on findings of a cervical root-level injury (spinal accessory [n = 1], long thoracic nerve [n = 1]).

The average length of surgery was 165 min (range, 50-250 min). There were no intraoperative complications, and all patients were extubated prior to leaving the operating room. The average number of days for postoperative hospitalization was 2 (range, 1-4 days). Postoperative complications consisted of an infection at the sural nerve harvest site in one patient who was effectively treated with antibiotics, whereas there were no incidences of postoperative pneumonia or respiratory complications.

In six of the seven patients with partial denervation injuries, there was an SF-36-reported improvement noted in the first 3 months postoperatively that was verified on sniff testing and PFTs (Fig 1, Table 1). One patient in this group underwent postoperative NCS/EMG testing at 6 months, which revealed a 69% improvement in compound motor action potential response (0.14-0.31 mV [reference, $\geq$0.33 mV]) and a 47% reduction in conduction latency (11.2-10.1 milliseconds [reference, 8.0 ± 1.5 milliseconds]).

Three of the five patients with complete denervation injuries reported SF-36 improvements between 8 and 14 months postoperatively, two of whom demonstrated improved diaphragm motion on sniff testing and improvements in both FEV_1 and FVC (Table 1). In four patients, respiratory improvements could not be well documented; one died of a cardiac event before additional testing could be performed, and two were too early in their postoperative course for evaluation. The fourth patient, in whom recovery could not be documented, had a persistent paralysis of the diaphragm on sniff testing at 8 months following surgery.

The mean preoperative FEV_1 and FVC for all 12 patients was $62\% \pm 29\%$ and $65\% \pm 32\%$, respectively. In the nine patients who underwent both preoperative and postoperative spirometry, FEV_1 and FVC improved following treatment by an average of $12\% \pm 13\%$ and $12\% \pm 17\%$, respectively (Table 1).

Overall, nine (90%) of 10 patients evaluated with the SF-36 demonstrated clinical respiratory improvements, eight of whom could be confirmed with PFT and sniff testing. Comparative fluoroscopic sniff testing demonstrated an unequivocal improvement in diaphragm motion in eight (89%) of nine tested.

Discussion

The phrenic nerve is a peripheral nerve originating from roots C3 to C5. On each side of the body, the nerve courses in the neck through the mediastinum and innervates the hemidiaphragm on that side. Injury to the nerve may occur from surgery, anesthetic blocks, trauma, or manipulation performed in the neck and chest. Unilateral phrenic injury may result in atelectasis, pneumonia, decreased pulmonary function, sleep-disordered breathing and pulmonary effusion due to paralysis of the hemidiaphragm.[1,5-7]

Neuronal injury as described by Seddon[16] can be divided into three types: neurapraxia, a temporary dysfunction; axonotmesis, an interruption of axons with preservation of the supporting structures; and

Table 1—***Demographics and Outcomes of Patients Undergoing Diaphragm Reinnervation Surgery***

Patient No.	Age, y	Sex	Side	Etiology	Injury	Duration	Treatment	Follow-up, mo	SF-36	PFT, %		Sniff
										ΔFEV_1	ΔFVC	
1	40	M	L	B	Complete	9	NL, IG	38	+	+15	+16	+
2	53	M	L	B	Partial	31	NL	12	+	+17	+22	+
3	52	M	L	S-ND	Partial	8	NL	27	+	+16	+13	+
4	57	M	R	S-CB	Complete	72	NL, IG	16	+	+6	+7	+
5	47	M	L	C	Partial	26	NL	20	+	+25	+29	+
6	56	F	L	S-TO	Partial	12	NL, IG	14	+	+14	+12	+
7	68	F	R	S-CB	Partial	9	NL, IG	15	+	+5	+4	+
8	59	F	L	C	Partial	35	NL, IG	16	+	+10	+6	+
9	47	M	L	S-ND	Complete	64	NL, IG	8	…	0	−2	…
10	54	M	L	S-CBG	Complete	18	NL, IG	10[a]	+	n/a	n/a	n/a
11	64	F	L	T	Partial	60	NL, NT	5	n/a	n/a	n/a	n/a
12	53	M	R	T	Complete	18	NL, NT	4	n/a	n/a	n/a	n/a

B = anesthetic block; C = chiropractic manipulation; F = female; IG = interposition graft; L = left; M = male; − = no improvement following treatment; n/a = testing was not performed; NL = neurolysis; NT = neurotization; PFT = pulmonary function test; + = an improvement following treatment; R = right; S-CB = carotid bypass surgery; S-CBG = coronary bypass graft surgery; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; S-ND = neck dissection surgery; S-TO = thoracic outlet surgery; T = trauma.
[a]Died.

neurotmesis, a destruction of all essential parts of the nerve. One of the most serious sequelae of cardiac surgery is injury to the phrenic nerve. Reported incidence varies because it is postulated that only 50% of affected individuals manifest symptoms.[17,18] The injury most often occurs during harvesting of the left-side internal mammary artery and is more likely a neurotmesis-type injury from partial or complete transection. Alternatively, thermal injury may occur during cardiac hypothermia, precipitating axonotmesis because it is more likely that the nerve sheath will remain intact. Both neurotmesis and axonotmesis are likely to result in irreversible nerve damage, reducing or eliminating the possibility of spontaneous recovery, whereas neurapraxia typically will recover without therapeutic intervention. Distinguishing patients whose paralysis will recover spontaneously from those who may benefit from surgical intervention usually is possible by assessing results of NCS/EMG testing and performing serial evaluations over a period of approximately 6 months from the time of injury to look for interval improvement.

For those patients with unilateral phrenic injuries that will not recover spontaneously, therapeutic options are extremely limited. The only therapy currently being performed commonly is plication of the diaphragm, a procedure that flattens the diaphragm in its inspiratory position. Plication has been studied more extensively in the pediatric population because diaphragmatic paralysis rarely spontaneously resolves in this patient population. Respiratory insufficiency seems to persist in younger patients, necessitating the procedure in infants, although it traditionally has been believed that older children have a higher tolerance for a unilateral diaphragm paralysis. Despite being a viable therapy in the pediatric population, diaphragm plication is an invasive procedure, and long-term relief of symptomatic phrenic nerve injury is questionable in adults. Studies have shown recurrent elevation of the diaphragm in many patients, with up to 19% requiring additional surgery.[10,11]

Diaphragmatic pacemakers consist of phrenic nerve electrodes implanted in the cervical region or the thorax or direct electrodes placed in the diaphragm muscle using a laparoscopic abdominal approach.[19] They allow ventilator-dependent patients with tetraplegia to be maintained permanently or temporarily without the use of mechanical-assist devices. Freedom from the ventilator has been demonstrated to allow greater mobility, improved speech, improved overall health and quality of life, and reduced health-care costs. Unfortunately, diaphragmatic pacing generally is performed only in patients with bilateral nerve injury because current technology does not permit timing electronic impulses to physiologically derived respiratory activity.

Immediate repair of phrenic nerve transection has been described in the literature in scattered case reports.[13,20] Brouillette et al[13] reported immediate end-to-end anastamosis in an infant after teratoma resection. Krieger and Krieger[21] showed that the intercostal nerve can be used to neurotize the phrenic nerve in spinal cord injury when the level of paralysis involves the C3 to C5 region. There are also two reported cases that describe the sural nerve being used as an interposition graft to replace a 3-cm gap that resulted in a return of function demonstrated at 1 year.[12,13] Although success of long interposition grafts (≥20 cm) has not been previously documented in cases of diaphragm paralysis, several human and animal studies have supported the feasibility of using long nerve autografts for muscle reinnervation, with

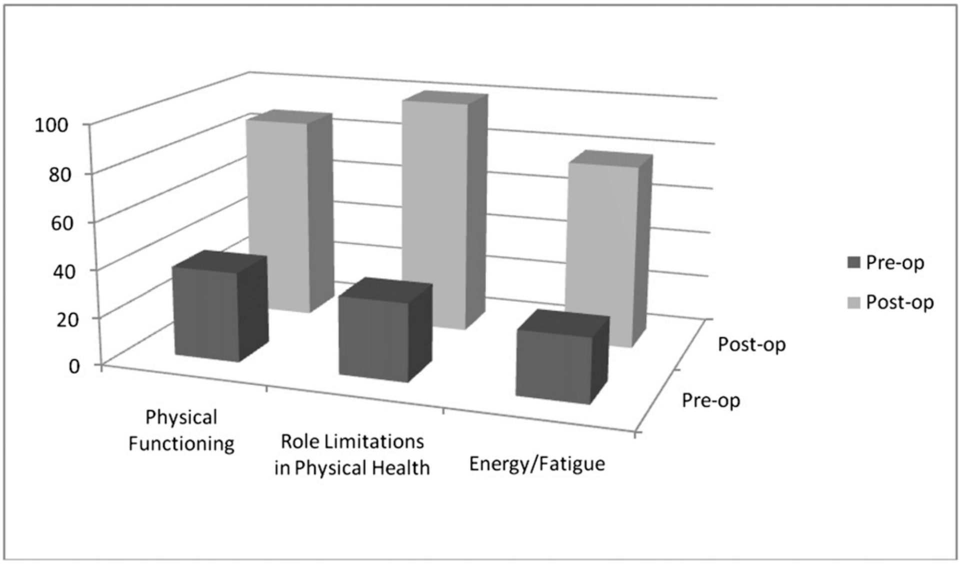

FIGURE 1. Results of the Medical Outcomes Study 36-Item Short Form Health Survey following diaphragm reinnervation surgery in symptomatic patients with diaphragm paralysis (n = 10; normal functioning, 100). Pre-op = before operation; Post-op = after operation.

success rates approximating those of short-segment nerve repair.[22,23]

In the present series, seven sural interposition grafts were performed, the indication being a complete denervation injury or when neurolysis alone failed to improve the threshold for conduction in patients with partial denervation injuries. On the basis of the traditional principle of peripheral nerve repair that nerves regenerate at 1 mm/d, it would be expected that long-segment interposition grafts would not provide clinical improvement for at least 6 months. Nerve regeneration rates frequently differ from established principles, and clinical improvement following a ≥ 20-cm nerve graft may occur more rapidly than expected, or alternatively, there may be an absence of clinical recovery for up to 18 months. Thus, a true clinical failure would not be documented unless the patient was well beyond this time period with no objective evidence of recovery. In our series, it is possible that recovery occurred more rapidly than expected when interposition grafts were used as an adjunct to neurolysis in cases of partial denervation. In this scenario, there could be limited recovery of function immediately from the neurolysis followed by enhanced function months later as the nerve graft begins to function. Although we cannot conclusively demonstrate this phenomenon in the current study, follow-up reports indicate the likelihood that it occurred in two patients.

In all patients who underwent neurolysis alone and in one patient who underwent both neurolysis and grafting, there was immediate clinical improvement. The basis for this improvement may have to do with the pathophysiology of the injury. It is believed that two of these patients sustained diaphragm paralysis following chiropractic manipulation, whereas the remaining two were from an epidural block and neck dissection, respectively. The clinical appearance and nerve conduction reports both suggest a reversible compression neuropathy not unlike any common compression neuropathy in the extremities (ie, carpal tunnel syndrome). Just as carpal tunnel release of the median nerve often results in immediate improvement in hand function, we hypothesize that "release" of the phrenic nerve can reverse diaphragm paralysis. Testing this hypothesis would require serial postoperative NCS/EMG testing on larger patient samples to measure conduction latencies and MUPs following phrenic nerve neurolysis. In the current study, we were able to document a reduction in conduction latency and improved MUP postoperatively in one patient. Because of the discomfort associated with NCS/EMG testing, all other patients refused to undergo repeat postoperative testing to merely corroborate clinical and radiographic findings.

Yoshitani et al[24] recently described a series of phrenic nerve repairs using nerve tubes in dogs, demonstrating that the diaphragm can regain function using neural tubes as a conduit for nerve regeneration, especially in the setting of a pericardial fat pad. In their series, the phrenic nerve was acutely transected and replaced with a 30-mm graft. By 4 months, three of the four dogs receiving the nerve tube placed in a pericardial fat pad had regained function. In the group without use of a pericardial fat pad, only one of five dogs regained function. In both groups, the phrenic nerve demonstrated its ability to regenerate; however, the fat pad greatly enhanced its potential. In the present series, we routinely wrapped the neural anastomosis with the pericardial fat pad in patients who required a thoracic approach for interposition grafting.

Interpositional nerve grafting and neurolysis have been described extensively in a wide array of nerve injuries.[25-27] These results have been encouraging, with many patients regaining motor function after transplantation. Successful nerve grafting depends on preservation of the potential for nerve conduction and the viability of motor end plates. Conventional teaching states that after 12 to 18 months of denervation, the motor end plates degenerate, thereby prohibiting the muscle from regaining function despite a nerve transplant. Contrary to this teaching, there are reports of nerve transplants well beyond this time period after initial injury that show recovery of motor function. Tadie et al[27] even described partial motor recovery with transplantation 3 years after injury, suggesting that not all motor end plates degenerate at the same rate and that the duration of time since initial injury alone should not preclude nerve transplant. Furthermore, in cases where there is partial denervation, the motor end plates may receive a subthreshold level of conduction, enough to maintain viability of the motor end plates despite an absence of diaphragm contractility. Thus, there may be an indefinite period of time during which reinnervation is possible.

The success rates in the present study are comparable to reports documenting functional recovery rates of approximately 90% and 75% in patients undergoing neurolysis and nerve grafting (or neurotizations) for paralysis of the upper and lower extremities, respectively.[28,29] Rates of clinical recovery following neurolysis generally are expected to exceed those of nerve grafting or neurotization based on the notion that patients requiring the latter have more severe injuries.

Conclusion

We report 12 cases of unilateral phrenic nerve injury treated with established nerve reconstruction techniques and propose that the algorithm we used be followed for treatment of this disorder. The results demonstrate that the procedures can be performed safely and with a high likelihood of clinical improvement. The reconstructive techniques are commonplace in peripheral nerve surgery, and the results of this small series support expanding their utility for paralysis of the diaphragm, a particular problem without an extensive array of current treatment options.

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Author contributions: Dr Kaufman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Kaufman: contributed to all phases of the research including data collection and assessment, performance of all procedures, and preparation and review of the manuscript.

Dr Elkwood: contributed to the research through involvement in surgical procedures, preparation and review of the manuscript, and development of surgical techniques.

Dr Rose: contributed to the research through involvement in surgical procedures and preparation and review of the manuscript.

Dr Patel: contributed to the research through participation in surgical procedures and preparation and review of the manuscript.

Dr Ashinoff: contributed to the research through participation in surgical procedures and preparation and review of the manuscript.

Dr Saad: contributed to the research through literature citations and preparation of portions of the manuscript.

Dr Caccavale: contributed to the research through involvement in surgical procedures and preparation and review of the manuscript.

Dr Bocage: contributed to the research through involvement in surgical procedures and preparation and review of the manuscript.

Dr Cole: contributed to the research through performance of all preoperative nerve studies, preparation of portions of the manuscript, and review of the completed manuscript.

Dr Soriano: contributed to the research through assembly of the pulmonary function test data and preparation and review of the manuscript.

Dr Fein: contributed to the research through assembly of the pulmonary function test data and preparation and review of the manuscript.

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Additional information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/140/1/191/suppl/DC1.

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