AMYOTROPHIC LATERAL SCLEROSIS (ALS) REMAINS A RAPIDLY PROGRESSIVE FATAL DEGENERATIVE DISEASE OF MOTOR NEURONS THAT LEADS TO MUSCLE PARALYSIS. DISEASE PROGRESSION IS TYPICALLY FAIRLY LINEAR, AND DEATH FROM RESPIRATORY FAILURE OCCURS 3–5 YEARS FROM ONSET. THERE CAN, HOWEVER, BE VARIABILITY IN PROGRESSION RATE WITHIN INDIVIDUAL PATIENTS AND ALSO IN SURVIVAL BETWEEN PATIENTS. UNFORTUNATELY, THERE ARE FEW EVIDENCE-BASED OPTIONS FOR SLOWING DISEASE PROGRESSION OR IMPROVING QUALITY OF LIFE FOR PATIENTS AFFECTED BY ALS.

BACKGROUND: PHRENIC NERVE PACING

Phrenic nerve pacing (PNP) has been sparsely used for decades as an alternative or replacement for invasive positive pressure mechanical ventilation (IPPV) in selected patients with severe chronic hypoventilation syndromes who have preserved (normal) phrenic nerves (e.g., high-level spinal cord injury). Several commercial devices are available. Unipolar or four-pole sequential stimulating electrodes are attached to the phrenic nerves, most commonly in the upper chest via thoracotomy, thoracotomy, or sternotomy, and then attached to subcutaneous radiofrequency receivers. An external stimulator controls the internal receiver via induction, so nothing pierces the skin. Low-frequency (<8 Hz) stimulation successfully conditions the diaphragm by changing the muscle fibers into slow-twitch, fatigue-resistant type over several weeks to months, and avoids stimulation-induced fatigue. Selected patients can use their PNP device for as long as 24 hours per day for ventilatory support and may be successfully weaned from mechanical ventilation.

There are no randomized, placebo-controlled trials of PNP. Carter et al. reported on a retrospective cohort at a single center by comparing ventilated spinal cord injury (SCI) patients with those breathing with PNP. Despite the small number of patients, PNP patients had a fourfold increase in average survival from SCI onset (48 months) compared with mechanically ventilated patients (13 months). Several case reports, retrospective case series, and 1 small prospective series have reported on outcomes of PNP in hypoventilation syndromes. Patients with PNP who are weaned from IPPV have reduced frequency of infections, improved quality of speech, improved olfaction, greater mobility, and improved quality of life, compared to patients with hypoventilation syndromes on IPPV. Failure to wean with PNP is associated with improper patient selection, diaphragm amytrophy, and malnutrition. Complications from PNP appear to be rare and include infection, atelectasis, pneumothorax, and device failure.

The U.S. Food and Drug Administration (FDA) approved a diaphragm pacing (DP) system for patients with ALS in September 2011. Although this new option is highly promising, there remains significant uncertainty in the community of ALS clinicians and scientists regarding the use of this system (R.B., personal communication). The purpose of this report is to review the background, available safety and efficacy data for DP in ALS, and the FDA-approval process for medical devices.

Abbreviations: AE, adverse event (not serious); ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; CMAP, compound muscle action potential; DP, diaphragm pacing; EMG, electromyography; EPS, Epworth Sleepiness Scale; FDA, U.S. Food and Drug Administration; FVC, forced vital capacity; IPPV, invasive positive pressure mechanical ventilation; LMN, lower motor neuron; NCS, nerve conduction studies; NIV, noninvasive ventilation; PFT, pulmonary function testing; PNP, phrenic nerve pacing; SCI, spinal cord injury. Key words: amyotrophic lateral sclerosis; diaphragm pacing; Food and Drug Administration; phrenic nerve pacing; spinal cord injury.

Disclosure: R.S.B. is a speaker for Avanir, Lilly, and Pfizer Pharmaceuticals, has consulted for UCB Pharmaceuticals, and has had recent grant support from Cytokinetics, Biogen, and Neuraltis Pharmaceuticals.

Correspondence to: K. Scherer; e-mail: kscherer@email.arizona.edu

© 2012 Wiley Periodicals, Inc. Published online 14 April 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.23419
METHODS

We performed a PubMed search with the following search terms: amyotrophic lateral sclerosis AND one of the following terms: diaphragm muscle, phrenic nerve conduction, diaphragm pacing, phrenic nerve pacing, electrical stimulation, forced vital capacity (FVC), survival, prognosis, and diaphragm AND muscle fiber type. Retrieved titles and abstracts were reviewed by 1 of the authors (K.S.) for relevance, and relevant articles were obtained in full text and reviewed by both authors. References in the full-text articles were reviewed for any additional relevant publications. Information was also obtained from the FDA website (http://www.fda.gov).

DIRECT DIAPHRAGMATIC PACING VIA INTRAMUSCULAR ELECTRODES

History of DP. Direct intramuscular electrical stimulation of the diaphragm was pioneered at Case Western Reserve University (Case) in the 1980s.19–21 The first human implantation resulted in successful conditioning and weaning from the ventilator full time in a high-level SCI patient.22 A major difference from PNP is the need to map the motor point on the underside of the diaphragm where the phrenic nerve branches are invisible.23,24 By 2009, more than 50 high-level SCI patients were successfully implanted, and commercial development led to the 2008 grant of a Humanitarian Use Device exemption from the FDA for the Synapse Biomedical NeuRx Diaphragm Pacing System (DPS) for the indication of stable, high-level SCI. The first ALS patient was implanted at Case in 2005.25

Description of the DP System. Two monopolar needle electrodes are inserted into the motor points of each hemidiaphragm via laparoscopy. The 4 stimulating electrode wires (cathodes) are brought out through the epigastric port (connection site), where they are connected to second-order wires that are tunneled subcutaneously in a silicone sleeve to an exit site in the subclavicular fossa.22,23,24 The reference electrode (anode) is inserted subcutaneously at the connection site and tunneled together with the 4 cathode wires. After exiting the skin, they can be plugged into a four-channel external stimulator (pulse generator) that delivers constant current stimuli. The stimulator controls the charge delivered through clinician-programmed parameters (stimulus amplitude, duration, frequency, and respiratory parameters of inspiratory duration and respiratory rate).26 Stimuli up to 24-mA intensity, 0.150-ms duration, and 50-Hz frequency have been used in usual train (inspiratory time) lengths of 1.1 seconds at a rate of 10–12 breaths/min.22,26–29 Response to stimulation is assessed intraoperatively by direct observation of diaphragm contraction and measurement of changes in abdominal pressure through one of the laparoscopic ports, and postoperatively by spirometry or fluoroscopy. Shoulder pain has been reported at high stimulus intensities or high-frequency stimulation, even in SCI patients who were anesthetic below their spinal cord injury level.22,26,30 Shoulder pain is a significant limiting factor in ALS patients, and it limits the strength of the electrical stimulation that patients can tolerate comfortably. SCI patients typically use a setting that delivers 15% over their required tidal volume.26 ALS patients use settings they can tolerate without significant discomfort. The stimulator is turned on in the immediate postoperative period for ALS and after 2 weeks in SCI patients. A gradual conditioning program similar to PNP is then used to improve the strength of the diaphragm, reduce fatigue, and gradually wean SCI patients from their ventilators.30 ALS patients may use DP more for diaphragm conditioning rather than as a means of primary negative ventilation.26

DP vs. PNP. The surgical risks in experienced hands should be similar, but no head-to-head comparisons of DP vs. PNP have been published. One disadvantage of DP is the lack of a fully contained subcutaneous system, and thus skin infections can occur at the electrode exit and connection sites.

Technical Considerations. The DP stimulating electrodes are 2.5-mm-long, 1-mm-thick monopolar needles that are inserted parallel to the diaphragm muscle fibers. The sheath inserting the needle is 1.6 mm thick. The thickness of the human diaphragm at the motor point is not known. Ultrasound studies have measured the appositional costal diaphragm at between 1 and 5 mm, depending on the inspiratory cycle,31 and diaphragm thickness may vary significantly by location along the muscle according to age, weight, and general health status.32 A study on excised cadaver diaphragms measured the average thickness at the motor point to be around 3 mm.32 ALS patients will have denervation atrophy and therefore thinner diaphragms, which can potentially complicate insertion and increase the risk of perforation and pneumothorax. Accessing the right hemidiaphragm motor point might be challenging during surgery due to its proximity to the liver and its frequent location near the inferior vena cava and within the central tendon.22,32

Data in SCI. The first SCI patient implanted was a previously healthy, 35-year-old man who had a high SCI due to a diving accident 1.6 years prior to implantation. The right hemidiaphragm...
electrodes were implanted too far from the motor point, and he underwent a second operation several months later to reimplant the right side. He successfully conditioned the diaphragm over the following months, and at 15-month follow-up he was using the DP system 24 h/day. The next 5 reported patients were all men, 180–200 lbs., implanted 1–8 years post-accident, who had baseline spontaneous vital capacities ranging from 280 to 890 ml, but with ventilator-free breathing ability of less than 1–2 h/day. One patient could not be paced because of a preoperative false-positive phrenic nerve study. Of the 4 who were successfully implanted and had achieved full conditioning, 3 were using DP full time, and another used it 20 h/day. All had stimulated chronic inspired volumes of 800–950 ml. Other reported benefits were re-establishment of olfaction, improved speaking, and improved quality of life.

A prospective cohort study of DP in SCI took place under an FDA Investigational Device Exemption program. The inclusion criterion was “chronic ventilator-dependent high-level SCI patient with stimulatable diaphragm.” Enrolled subjects were predominantly male (37 of 50), with an average age of 36 years (range 18–74 years) and average time since injury of 5.6 years (range 3 months to 27 years). Forty-nine of 50 enrolled subjects were successfully implanted; 1 could not be paced due to a denervated diaphragm. Ninety-eight percent of the subjects achieved the primary endpoint of a clinically acceptable tidal volume of ≥7 ml/kg for men and ≥6 ml/kg for women; 96% achieved the endpoint of using the DP stimulator and being off ventilators for >4 h/day with a median follow-up of 2 years postimplantation. In terms of adverse events, 21 of 50 subjects had capnothorax (air above the diaphragm) evident on postoperative X-rays, and 1 subject developed a wound infection. No other adverse events related to the DP stimulator or its implantation were reported. Ten patients with concurrent cardiac pacemakers were analyzed, and no device-to-device interactions were found. At the time of the 2009 publication, 5 of 50 subjects had died from causes unrelated to the DP stimulator or its implantation, and 44 of 50 subjects were using their device (not reported for how many hours daily).

**Data in ALS.** The first ALS implant occurred in 2005, and a poster on the first 16 ALS patients was presented in 2007. Seven of the 16 had simultaneous gastrostomy insertion. Average age was 50 (range 32–70) years, and 13 of 16 were men. The time from ALS onset in this cohort averaged 35 months, the ALS Functional Rating Scale—Revised (ALSFRS-R) averaged 26 points, and FVC averaged 52% of predicted at time of surgery (ranges not published). Twelve of 16 patients eventually developed bulbar dysfunction. This is the only mention of bulbar dysfunction to date in implanted ALS patients. In all patients, fluoroscopically measured diaphragm excursion was greater with DP than with maximal voluntary effort; ultrasound analysis of diaphragm thickness reportedly increased from pre-implantation values. Important details were lacking in the abstract, including intra- and inter-observer reliabilities, whether measurements were made by blinded observers, the definition of a clinically significant change, and the actual data. Subgroup analysis of patients with bulbar dysfunction prior to surgery showed that their average rate of FVC decline went from 2.4% per month to 1.4% after implantation. It is not clear why only this subgroup was selected for analysis, nor for how long they were followed, nor how much variability there was in this effect between patients. The first 4 patients, who had an average FVC of 49% of predicted at surgery, died at an average 16.5 months after implantation. One death each occurred from respiratory complications, aspiration, the effects of a fall, and complications of cervical spine surgery. This was said to represent an improvement in survival when compared with historical cohorts with the same average FVC, but the reference for the comparison group was not provided.

A 2009 paper summarized the worldwide experience with DP in ALS and divided patients into three cohorts. The first group was the cohort of 16 patients described earlier, who were said to be part of a “safety and feasibility trial.” The second group was 20 patients said to be part of a “pivotal trial,” with a plan for an additional 80 to be enrolled across multiple U.S. and French sites. This was not a conventional trial but rather an uncontrolled, non-blinded, prospective surgical cohort study. The paper lacks details on inclusion and exclusion criteria, which we obtained from the clinicaltrials.gov website: patients had laboratory-supported probable, probable, or definite ALS by El Escorial criteria; clinically acceptable phrenic nerve function as demonstrated by bilateral diaphragm movement with fluoroscopic sniff test or with electromyography (EMG) recordings and nerve conduction study (NCS); FVC of 50–85% predicted at enrollment; and >45% predicted at the time of surgery (http://www.clinicaltrials.gov, identifier NCT00420719). Patients with implanted cardiac pacemakers or defibrillators were excluded, as were patients with significant underlying cardiopulmonary disease. Patients were to serve as their own controls. They were evaluated 3 times prior to implantation and then every 4–12 weeks until 1 year from enrollment, but the exact timeline of
assessments was unclear. Clinical assessments included the SF-36 Health Survey, ALSFRS-R, ultrasonic measurement of diaphragm thickness, phrenic nerve conduction studies (NCS), fluoroscopic sniff tests, and pulmonary function testing (PFT). The final ALS group described in the 2009 paper consisted of 2 patients who did not meet the inclusion criteria of being >50% FVC at enrollment and received a DP stimulator via “compassionate use.”26 These 2 patients were reportedly evaluated by continuous EMG from the implanted diaphragm electrodes and by pulse oximetry. The authors mentioned that ALS diaphragms had weaker contractions during the mapping (compared with the SCI patients) and were often visibly denervated. Some ALS diaphragms did not move at all with single mapping stimuli and required 1-second burst stimulation to locate the motor points. Using burst stimuli and lowering the insufflation pressures allowed adequate mapping, and all patients were successfully implanted. Patients with “more upper motor neuron involvement” reportedly had better diaphragm excursion with DP stimulation by fluoroscopy; it is not clear how the amount of upper motor involvement was quantified. All ALS patients were extubated with the help of their newly implanted DP stimulator.26

The 2009 paper described the results of the first two groups of ALS patients implanted with DP stimulators separately; results from the third group of 2 patients were largely not described.26 Some of the results reported from the first group of 16 patients in the paper are different from those described in the same patients in the 2007 abstract. The average FVC at implantation in this group was now said to be 59% (previously said to be 52%). The rate of FVC decline was now said to have improved from 2.4% per month to 0.9% per month (previously said to have dropped from 2.4% to 1.4% per month). From this drop in FVC decline, the authors extrapolated a “24-month increase in survival.” They later stated that these patients “have delayed their need for a ventilator by up to 24 months,” but it is not clear how these claims were determined. The paper reported that DP converted fast-twitch to slow-twitch muscle fibers, improved lung compliance, decreased work of breathing, and improved nighttime ventilation; no details of the methods used were provided. The second group of 20 patients had an average age of 55 years, were 70% male, had a mean FVC 60% at the time of surgery, and were an average of 22 months from diagnosis at the time of surgery. No other results for this cohort were provided. No data on the SF-36 or ALSFRS-R were provided for any cohort. Among the 38 ALS patients implanted with DP systems, adverse events included 5 patients with capnothorax and 1 with a wound infection.

A second paper from 2009 provided further updates on the aforementioned cohorts.27 The first cohort of 16 ALS patients with DP systems was described differently compared with prior reports. This time, the average FVC was said to be 56% (previously, 52% in one report and 59% in another), and 6 had simultaneous gastrostomy placement (previously reported as 7). More details were provided on the “compassionate use” cohort of 2 ALS patients: they had FVCs of 26% and 28% of predicted, and both had simultaneous gastrostomy placement. By the time of this report, the “pivotal trial” cohort had increased to 33 ALS patients. The mean age in this cohort was 55 years; 67% were men. The mean FVC at surgery was 60% (range 45–87%) of predicted. The authors reported zero 30-day mortality, and all patients were extubated successfully postoperatively. No other outcomes were reported.

Three of the ALS patients from the “pivotal trial” cohort who were implanted at the Stanford University site were reported separately.33 Few clinical demographic data were presented; their ages were 42, 63, and 38 years, and all were wheelchair bound with FVC >50%. Simultaneous gastrostomy tubes were inserted in all patients after DP system implantation. One patient had a previously undiagnosed dilated cardiomyopathy and developed ventricular tachycardia postoperatively, resulting in an unplanned 12-day hospital stay. No efficacy outcome data were presented.

ALS patients from the “pivotal trial” cohort who underwent implantation at the French site were part of an ancillary study of the effects of DP on sleep.34 Of 24 enrolled patients, 1 died before implantation, 1 withdrew consent, and 4 had a fall in FVC to <45% predicted and were thus excluded from implantation per protocol, resulting in 18 patients studied. In addition to outcomes for the “pivotal trial” (described earlier), the Epworth score and overnight polysomnogram were obtained immediately before and 4 months after DP system implantation. Sleep stages, arousals, and respiratory events were scored visually. It is not clear whether the scorers were blinded to the study visit. Only 14 of 18 completed both of these study visits, as 2 patients died, 1 was lost, and 1 withdrew consent. Missing data were imputed in an unusual manner: “non-informative” data (“not relating” to the outcome under study) were imputed with the median of observed data, and “informative” data (“possibly related” to the study outcome) were imputed with the 10th or 90th percentile, whichever was worse relative to the median. The imputing process reportedly “had minimal effects on the significance levels when comparing...observed versus imputed data.”
but results did not confirm this. Nine of 18 patients were using noninvasive ventilation (NIV) throughout the study period; no changes in NIV (new starts or settings) reportedly occurred between study visits. The investigators reported a statistically significant reduction in arousal index and a statistically significant improved wake after sleep onset (defined as the percentage of time spent awake after sleep onset). There was also a small improvement in overall sleep efficiency from 69 ± 15% to 75 ± 11%, but this did not remain statistically significant after correction for multiple comparisons. They reported no data on quality-of-life measures. No significant change was observed on the Epworth Sleepiness Scale, apnea/hypopnea index, amount of nighttime hypoxia, or sleep architecture. To date, this is the only published full-length paper that reports data on disease progression in ALS patients who received DP stimulators; ALSFRS-R declined an average of 1.22 points/month, and predicted FVC declined 2.35%/month. There is no comparison between changes in the reported "pivotal trial" outcome measures in the pre-implantation period compared with the post-implantation period.

In its 2011 report to the FDA, Synapse Biomedical updated information on the aforementioned cohorts (Summary of Safety and Probable Benefit, http://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006b.pdf). A total of 144 patients were enrolled, and 106 were implanted. The reasons for 38 enrolled patients not implanted were not well described. Safety outcome data were reported on “86 implanted patients who met the Humanitarian Use Device Group definition and were not otherwise excluded,” and efficacy data were reported on 84 patients (with 2 lost to follow-up). The reasons for the exclusion of 20 implanted patients from these reports were also not well described.

In terms of safety, serious adverse events (SAEs) considered to be related to DP system implantation occurred in 3 of 86 (3.5%) patients. These included: (1) capnothorax requiring intravenous catheter and an extended hospital stay; (2) capnothorax requiring intraoperative placement of an angiocatheter; and (3) respiratory failure after complications from surgery. Another patient had a serious reaction to anesthesia during implantation, and thus the procedure was aborted. SAEs not considered to be related to implantation (excluding the endpoints of death or tracheostomy) occurred in 36 of 86 (42%) patients, for a total of 61 events (average 1.7 events/patient). The most frequent was 8 patients (9%) with 11 episodes of pneumonia, and the others were in <2% of patients. Nonserious adverse events (AEs) were seen 8 of 86 (9.3%) patients with mild–moderate exit-site infec-

the FDA REGULATORY PROCESS

The FDA ensures the safety and effectiveness of drugs, vaccines, and other biological products and medical devices (http://www.fda.gov). The drug-approval process costs millions of dollars and it can take decades from initial in vitro experiments to getting a drug on the market. Large prospective, randomized, double-blind, controlled clinical trials with hundreds, sometimes thousands, of patients are typically necessary to prove drug safety and
efficacy and obtain FDA approval for marketing. Medical devices do not undergo such rigorous scientific testing. Some devices deemed minimal risk (Class I and II) do not undergo any scientific clinical testing before being put into routine clinical use (e.g., latex gloves, pregnancy tests, dental implants) and only require Premarket Notification (a.k.a. “510k”). Higher (a.k.a. Class III) risk devices (e.g., stents, joint implants) are normally required to undergo systematic testing to prove safety and efficacy, but the requirements are not as stringent as for drugs. The FDA provides another way for Class III devices to get market approval with little or no scientific testing through its Humanitarian Use Device exemption program (http://www.fda.gov). A humanitarian use device is one that is intended for patients with rare diseases, where the development costs of a device would be prohibitive. Such a device is exempt from the effectiveness requirements. It may only be used in facilities where a local institutional review board has approved the use of the device to treat or diagnose the specific disease. The labeling must state that the device is a humanitarian use device and that, although the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated.

**DISCUSSION**

DP for ALS has evolved logically from work with PNP and later DP in patients with SCI. Thus far, however, all scientific reports on DP for ALS have flaws that complicate interpretation. All reports are small, non-randomized, cohort studies. Given that the intervention is a surgery, it is easy to imagine that there may have been some selection bias, with overall healthier ALS patients being referred. Also, because ALS patients had to have both FVC 50–85% of predicted at enrollment and FVC >45% at implantation, there may have been selection bias favoring slower progressors. Such bias would limit generalizability of any safety or efficacy findings. Important baseline demographic descriptions of specific individual cohorts differ across different publications by the same author (e.g., average baseline FVC). Methodological details on how some of the outcomes were measured and validated have not been well described (e.g., fluoroscopically measured diaphragm excursion and ultrasound analysis of diaphragm thickness). Two types of “controls” have been used in the DP system cohort studies. First, patients have been their own controls, with outcome measures being obtained at several visits before and after DP system implantation. Unfortunately, the only outcome measure with rate of decline reported across pre- vs. post-implantation visits is FVC. An improvement in the rate of FVC decline between pre- and post-implantation has been reported for 1 small cohort, and this has been extrapolated to predict an improvement in survival. However, the size of the reported improvement in rate of decline in FVC in the same cohort of 16 ALS patients was different in 2 publications by the same author. Furthermore, prior studies have shown that respiratory scores may not always decline in a linear fashion in ALS, and comparisons of slopes at different time periods or extrapolations are difficult. A historical control (a subset of a cohort described in the Lo Coco study) was utilized in some of the reports, but it is not clear how it was selected, nor what matching was done to ensure that it was appropriate (Summary of Safety and Probable Benefit). In another ALS study of the effect of NIV on survival, patients who tolerated NIV >4 h/day and had a mean FVC of 45% at study entry had a median survival from NIV initiation of 18 months. This is comparable to Synapse Biomedical’s report of 19 months from DP system implantation. The proportion of ALS patients with significant bulbar involvement in the Lo Coco study was 21% vs. 24% in the Lechtzin et al. study. The proportion of bulbar involvement in the Synapse Biomedical dataset is unknown.

Besides survival, several other validated outcome measures were reportedly gathered at multiple visits before and after DP system implantation. It is unclear whether any of these were obtained in a blinded way. Some of the outcome measures reportedly obtained were never reported (e.g., SF-36 Health Survey). The meaning of some of the “positive” outcomes is not clear. For example, we do not understand the importance of reduction in arousal index and improved wake after sleep onset when there is no improvement in overall sleep efficiency. Enrolled and implanted patients appear to be lost or ignored in some of the analyses (Summary of Safety and Probable Benefit).

The usefulness of DP and negative pressure ventilation in patients with progressive bulbar dysfunction is not addressed in any of the aforementioned reports. Bulbar dysfunction develops eventually in most ALS patients; it limits the usefulness of NIV and likely that of DP. Demographic data regarding the presence of bulbar dysfunction were not presented in the reports discussed. There is a single mention that ALS patients with “more upper motor neuron involvement” had better diaphragm excursion with DP by fluoroscopy. There are no data on the
demographics of the authors’ patient population with regard to upper and lower motor neuron involvement. In theory, ALS patients with pure or predominant upper motor neuron syndromes could benefit from DP, but this needs to be investigated in appropriately designed clinical trials.

Patients with progressive lower motor neuron (LMN) degeneration will lose phrenic nerve function and diaphragm contractile ability, and at some point they will not benefit from DP. There are no details provided in any of the aforementioned reports with regard to what constitutes “acceptable phrenic nerve function” in ALS for the purpose of diaphragm stimulator implantation. Denervation on needle EMG in the diaphragm and paraspinal muscles correlates with FVC <80%. In a study of 29 ALS patients without clinical symptoms or signs of respiratory dysfunction and 30 controls, the phrenic CMAP was found to be reduced significantly with an increased phrenic latency. 44 Motor latencies, but not CMAP amplitudes, correlated with FPT. ALS patients had significantly abnormal spirometry. 45 ALS patients with 30% had clinical respiratory dysfunction, but non-selected ALS patients, Singh et al. reported significantly abnormal PFT. In their study of 43 ALS patients without clinical onset of respiratory dysfunction. The degree of axonal loss as measured by phrenic NCS may or may not correlate with respiratory function. This makes it difficult to judge which ALS patients might benefit from DP, or whether phrenic NCS can be used at all as a diagnostic or therapeutic biomarker. It seems from the description of the DP system study protocol that valuable data on respiratory parameters, phrenic NCS, and diaphragm EMG exist on these ALS patients, and we look forward to the publication of those results to improve our understanding of the relationship between phrenic nerve conduction abnormality and respiratory function in ALS.

Based on the data available, the DP system seems reasonably safe short term in carefully selected ALS patients with strict inclusion/exclusion criteria. We found no information on long-term safety. As ALS diaphragms undergo atrophy due to denervation, one possible concern is that the needle electrodes could migrate and pierce the diaphragm, causing pneumothorax or injury to abdominal organs. Due to the progressive nature of ALS and progressive denervation atrophy, long-term safety data from SCI patients is not translatable to ALS. Future systematic investigations of DP in ALS are necessary to understand the real-life short- and long-term risks and benefits.

REFERENCES

24. Onders RP, DiMarco AF, Ignagni AR, Mortimer JT. The learning curve for investigational surgery: lessons learned from laparoscopic...


