Amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease is a progressive neurodegenerative disease of unknown cause that results in the death of upper motor neurons (UMNs) in the brain and lower motor neurons (LMNs) in the brainstem and the spinal cord. Although ALS has no direct effect on the lung, it adversely affects the mechanical function of the respiratory system through LMN degeneration, leading to axonal degeneration of the phrenic nerve with subsequent loss of the major muscle of inspiration, the diaphragm. Progressive respiratory muscle weakness in ALS leads to carbon dioxide retention and hypercarbic respiratory failure – the major cause of death in ALS. The average life span of untreated patients from the time of onset is approximately 3 to 5 years. This is a multifaceted problem, led, in many cases, by decline in diaphragm function. The diaphragm provides around 70% of inspiratory functions in physiological normal individuals during awake, restful breathing. At the time of
sleep, the diaphragm normally provides more inspiratory motor mechanics, to the point of 100% during rapid eye movement (REM) sleep. The central drive for breathing is generated from a variety of sources. Volitional breathing can be generated from the motor cortex (UMN). Automatic breathing is generated from respiratory centers in the mid-brain. Finally, additional breathing control arises in the prebotzinger complex in the brainstem, which is one of the few UMN control systems in the brainstem. In ALS, patients have significant variabilities in UMN and LMN respiratory involvements, while both can lead to the same resultant respiratory failure.

Previously, the only recommended ways to overcome the loss of respiratory functions because of the loss of UMN control of ALS patients were to utilize noninvasive ventilation (NIV), commonly referred to as bilevel positive airway pressure, or tracheostomy with mechanical ventilation. Ventilators, although lifesaving, are only used by a very small percentage of patients. Alternate therapy to prevent or manage respiratory muscle decline in ALS was needed. Neurostimulation has been used for many years to assist dysfunctional muscle by replacing the lost drive signal from the central nervous system (UMN involvement). The technique of applying stimulation to elicit muscle contraction, whether using intramuscular or nerve cuff electrodes, requires that the nerve supply, ie the LMN, to the muscle is at least partially intact. The stimulation propagates along the nerve to create a coordinated contraction.

Diaphragm pacing (DP) involves laparoscopic mapping of the phrenic branches in each hemidiaphragm to identify optimal points where stimulation can provide maximal contraction of the diaphragm. DP was initially developed for spinal cord injured (SCI) patients who have complete UMN loss of control of their phrenic LMNs. DP has proven to be of significant benefit in allowing SCI patients to be liberated from the ventilators, thereby significantly improving their quality of life and decreasing their cost of care. Importantly, for the application of DP in patients with ALS, was the ability to reverse the disuse atrophy and convert Type Iib fast twitch muscle fiber to better functional Type I slow twitch muscle fiber. This muscle conversion was demonstrated in SCI patients, even in those with injuries exceeding 20 years.

The DP pilot trial was initially started to assess the safety and effects in ALS patients and it subsequently formed the basis for the multicenter pivotal trial that led to US Food and Drug Administration (FDA) approval of DP as a therapeutic option in ALS patients. This report analyzes the final outcome of the initial pilot patients.

Methods

This is a prospective open-label evaluation of all ALS patients implanted with the diaphragm pacing system (DPS, Synapse Biomedical, Oberlin, OH) during the initial pilot trial at the single investigational center of University Hospitals Case Medical Center, Cleveland, Ohio. This was performed under FDA Investigational Device Exemption G040142 and the Institutional Review Board approved the investigations. The study was registered at www.clinicaltrials.gov with the specific identifiers NCT00420719. Each patient had 3 extensive lead-in assessments that continued post DP implantation. The assessments included pulmonary function tests, fluoroscopic evaluation of diaphragm movement, ultrasound analysis of diaphragm thickness, and quality-of-life tests. Patients underwent outpatient laparoscopic diaphragm mapping with electrode implantations. The method of implantation and perioperative management of these initial patients have been previously described. Stimulus/output characteristics of each electrode were determined and diaphragm conditioning initiated. Patients conditioned their diaphragms with 5 daily stimulation sessions of 30 min each, but were allowed to increase the usage.

Results

From March 2003 to March 2007, 16 patients were implanted (3 women and 13 men) with an average age of 50 years (range: 32 to 70). The median time at enrollment since diagnosis of ALS in the patients was 19.6 months, with a median of 37.3 months since first onset of symptoms. Four patients initially presented with bulbar symptoms and 8 patients developed bulbar symptoms later. The median forced vital capacity (FVC) at enrollment was 65% predicted and at implantation 57% (range: 45% to 89%, with five below 50%). The average operative time was 98 min (range: 60 to 134), with no perioperative or unanticipated device-related adverse events. One patient had a pre-existing percutaneous endoscopic gastrostomy (PEG) tube and 5 patients had PEG tubes placed at the time of DP implantation, for a total of 6 PEG tubes at the time initial surgery. One additional patient had a PEG tube placed in the post DP period for a total of 7.

All of the patients had a phrenic nerve conduction study performed before enrollment to confirm intact phrenic nerves. On the left side of the patient, the average amplitude was .3 mV (range: .2 to .6), with a latency of 7.3 ms (range: 5.1 to 10.8). On the right side of the patient, the average amplitude was .3 mV (range: .1 to .6), with an average latency of 7.7 ms (range: 5.5 to 11.0). This test was used to confirm if patients had a stimulatable diaphragm with intact LMN, while there was a significant difference in the amount of functional muscle as illustrated by the wide range of amplitudes.

No patients stopped DP use because of pain, discomfort, or failure of implanted electrodes. The programmed stimulus for the majority of patients implanted during this study has been far below the maximum output of the stimulator. Initial programmed stimulus amplitude was adjusted to patient comfort during the conditioning sessions. The average stimulator output values used in the pilot trial were 13 mA and 135 µs, respectively, yielding an average charge density of .09 µC/mm² (range: .01 to .18 µC/mm²).
Creatine kinase (CK) and excess calcium (Ca) were used as primary physiological indicators of safety-related degradation of muscle in the study patients. A significant increase in CK or Ca post implant would indicate a safety concern. There were no significant increases in CK or Ca levels from pre to post implant and in most cases a slight declining trend.

Diaphragm thickness was measured using ultrasound at each of the study dates. Measurements were made of each hemidiaphragm during inspiratory and expiratory phase of normal voluntary (eg nonstimulated) respiration. The same operator, blinded to surgical implant, was used throughout the study to take the measurements to avoid any operator bias. All measurements were pooled across patients and study dates to assess pre- and postimplant diaphragm thickness. In all cases, the postimplant thickness was greater than the preimplant thickness (Table 1).

Fluoroscopic evaluation of voluntary maximal diaphragm excursion was performed at the time of enrollment. It was recognized that this test would be valuable in determining the extent of voluntary maximal contraction performed by a sniff test versus that of stimulated contraction of the diaphragm. Diaphragm contraction resulting from stimulation would highlight the loss of UMN control of the diaphragm with intact LMN. Through qualitative assessment, the visual observations identified that the stimulated diaphragm excursion was greater than the maximal voluntary diaphragm excursion in most cases.

The primary mechanism of action of DP is the conditioning of the diaphragm to effect respiration. The effectiveness of this action is measured using pulmonary function tests that can only be performed without DP being used. Efficacy of DP was determined by the comparison of the rate of respiratory decline pre and post implantation. The rate of respiratory decline was calculated on the basis of the percentage of predicted FVC on those patients with sufficient treatment data to accurately calculate a slope. In the final analysis, this totaled 13 subjects with 1 patient excluded, who was diagnosed with colon cancer post implant requiring another operation and further therapy. Slopes were calculated for each patient pre- and postimplant treatment and a paired t test was performed to identify the significance of the difference. The slope of decline for preimplant treatment was $-2.38 \pm 2.84\%$ per month, while it was $-1.34 \pm 1.49\%$ per month for postimplant treatment. The paired FVC rate of decline (treatment - lead in) improved with DP $1.04 \pm 2.35\%$ per month ($P = .14$) showing a decrease in decline. Although not meeting statistical significance, the trend was promising.

Although it would have been expected that improvements in diaphragm function would be reflected in an improvement in maximal inspiratory pressures, they did not show a significant change in the progression ($P = .88$). We suspect that this may be largely because of the difficulty in obtaining determinations of maximal inspiratory pressures in patients with bulbar dysfunction in ALS. The majority of patients studied had bulbar involvement, either at baseline or developed during the study. Arterial carbon dioxide levels all trended in the direction of improvement with treatment decreasing the rate of hypercarbia (slope of rise of $0.46$ pre implant to $0.24$ post implant for a $P$ value of $.16$).

Two primary instruments were used to assess the impact of the DP device on the patients’ quality of life. The ALS-revised functional rating scale is recognized as an important indicator of survival and component of ALS clinical studies. The revised version contains 3 respiratory status questions. The SF-36 is a multidimensional instrument that also provides quality-of-life measures. Slopes were calculated for each patient pre and post implant and a paired t test was performed to identify the significance of the difference. There was no statistically significant adverse effect of DP on the quality of life.

There have been a total of 452 implant-months of follow-up, with an average of 28.2 months per patient post implant. There were no internal electrode failures and a total of 7 external electrodes had to be repaired. This is out of a total 5 percutaneous electrodes per patient for a total of 2,260 months of total percutaneous wire exposure. All of these breaks were at the external connector holder and were repaired in an office setting. One patient required an oral antibiotic for a superficial wound infection. There were 5 reported respiratory infections requiring antibiotics.

All patients have expired with the last patient expiring in 2012; 72 months post implant using DP full time until his death with terminal weaning of DP. Median survival was 19.7 months from DP implant, 39.5 months from diagnosis, and 51.1 months from initial onset (Fig. 1). NIV was never used by 7 of the 16 patients and 50% of patients used DP during sleep when the implanted electrodes showed evidence lack of central drive consistent with acquired central sleep apnea. The cause of death or tracheostomy mechanical ventilation include respiratory failure (5 patients or 31% of all events), traumatic fall (1) aspiration (3), perioperatively from a cervical spinal fixation (1), urosepsis (1),

<table>
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<th>Test location (hemidiaphragm/position)</th>
<th>Thickness (mm)</th>
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<th>Postimplant</th>
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<tr>
<td>Right @ expiration</td>
<td>3.8 $\pm$ 0.9</td>
<td>4.7 $\pm$ 1.1</td>
<td>.01</td>
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</tbody>
</table>
Colon cancer (1), and terminal wean of DP in which 4 patients discontinued DP during final hospice care.

**Comments**

Long-term analysis of the DP system in ALS showed no safety issues. The pilot data suggest that DP can positively influence diaphragm physiology, respiratory functions, and survival in ALS patients. DP appears to affect the decline in respiration in ALS by artificially replacing or supporting the affected pathways in a similar way the DP overcame the loss of control in SCI patients. In this pilot study, it became obvious that the LMN pathways to the diaphragm were not lost on an all or none basis. It also became clear, with the first implanted ALS patient, that there was a combination of UMN and LMN involvement. Operatively, innervated (DP will positively effect) and denervated (DP will have no effect) diaphragm muscle fibers were visualized. Observations during testing showed that a DP stimulus had the ability to move more diaphragm than the patient could move volitionally. Thus, DP can improve respiratory functions in ALS by artificially replacing or supporting the affected pathways.

An interesting unanticipated finding during the study was the effect of DP on the subjective sleep disordered breathing in the implanted patients. Several patients began to use the device during sleep and reported reduction in sleep dysfunction. Analysis of overnight pulse oximetry and diaphragm electromyography showed that DP could overcome the incidence of hypopnea. Even with nocturnal NIV use, hypoventilation was identified. The addition of DP to NIV eliminated hypoventilation. This positive effect on sleep was further studied by Gonzalez-Bermejo et al., who showed significant sleep improvement after just 4 months of DP conditioning through an increased sleep efficiency with a reduction in arousal index driving a decrease in wake after sleep onset.

The results of this pilot trial lead to a multicenter pivotal trial with subsequent FDA approval of DP for ALS patients in 2011 under humanitarian device exemption for orphan diseases. The expected ALS patients for DP should have evidence of a stimulatable diaphragm by voluntary contraction or phrenic nerve conduction studies (to identify intact LMN) and who have chronic hypoventilation. Implantation should utilize general anesthesia performed with the techniques developed in this trial involving the use of short-acting narcotics and no neuromuscular blocking agents. The FDA summary of safety and probable benefits of DPS concludes the following: “DPS surgery was safe (infrequent serious adverse effects); DPS use was safe and well tolerated (no serious adverse effects)... Evidence of probable benefit includes a significant improvement in survival from diagnosis (by 16 months) and from the start of NIV (by 9 months) compared to standard-of-care NIV; a remarkable 100% 30-day survival rate of patients with simultaneous PEG and DPS compared to 30-day mortality expectations of 2% to 25% with continued long term improvement in survival; a 16 month survival from implant for patients with no other respiratory options that are intolerant or unable to use NIV; and statistically and clinically significant improvement in sleep.”

There is currently a dearth of treatment options available for ALS patients. The only approved drug to slow the progression of ALS, Riluzole, is a glutamate inhibitor which adversely affects the function of the central respiratory center response to hypoxia and offers a modest survival benefit of approximately 3 months. NIV is currently the first line of treatment for patients experiencing symptoms of respiratory insufficiency, but it is difficult to tolerate in some ALS patients. Gastrostomy tubes are also utilized in many ALS patients and when combined with DP it decreases the 30-day mortality rate. DP benefits ALS patients with primary UMN involvement of the diaphragm delaying the need for tracheostomy ventilation. Since most patients in the United States do not pursue tracheostomy ventilation, DP prolongs functional life. Although the pilot study was not randomized or matched to historical controls, given the median survival of 19.7 months with the average FVC at only 57% at implantation it gives a good indication of survival. Only 1 patient expired in the first year and most lived up to 12 to 36 months post implant with 1 using DP 6 years post implant.

In conclusion, surgeons need to be aware of the options available to ALS patients since 2 of the 4 therapies for patients with ALS can require the services of a surgeon. Offering therapies to maintain quality of life such as gastrostomy tubes for nutrition and DP for breathing are ways to help patients with this devastating disease.

**References**


Discussion

Robert Sticca (Grand Forks, ND): As Dr Onders said, this report describes the final analysis with trial for diaphragmatic stimulation in a terminal degenerative neurological disease, ALS. I have a couple of questions. As you said, your improvement in survival was about 16 months with the use of diaphragmatic pacing. What is the normal survival in these patients once they begin to experience respiratory effects? What is the normal thickness of the diaphragm? And you used it as a sort of a measure for conditioning of the diaphragm. Is it possible to have a totally implantable system?

And, lastly, what is the cost of the procedure and the cost per year of additional life? Does it compare with other current methods of mechanical replacement of organ function, such as things like hemodialysis?

Onders: There is a reason I picked a surgical oncologist to review my paper, since a lot of our curves are very similar to your oncology survival curves. For your first question, once your forced vital capacity gets less than 50% without any therapy, be it non-invasive ventilation or diaphragm pacing, the survival approaches zero at 9 months. So, actually, 5 of our patients had a forced vital capacity of less than 50 at surgery. And, obviously, they continued living quite longer afterwards. The normal diaphragms had diaphragms between 3 to 5 millimeters. We actually did an autopsy study looking at that and presented this at the Midwestern Surgical Meeting in 2003. Can it be totally implantable? If you have a lot of money, yes, it can but for an orphan disease like ALS that is not financially viable.

For your last question concerning cost benefit, we believe it does. The cost for the device is 20,000. So you add an operation, it’s about 25,000. The cost of being on a ventilator per year in the United States is $150,000. In the United States, only about 5% of ALS patients choose tracheostomy mechanical ventilation. In other countries it can approach 90%. And so we actually know the cost effectiveness in other countries where this is being performed can have significant cost saving. Our spinal cord data is tremendous in cost effective data. In the United States the cost savings may not be as large because most patients do not go on ventilators but the ability to breath for over an additional year is significant.