Respiratory Effects of Amyotrophic Lateral Sclerosis: Problems and Solutions

Noah Lechtzin MD MHS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease. Most patients die from respiratory complications. Fortunately, there are a growing number of treatment options that can improve both survival and quality of life for patients with ALS. This review discusses the respiratory evaluation and treatment of patients with ALS, about which a great deal is known. It also includes material on related problems, such as speech and swallowing difficulties and end-of-life care. *Key words: ventilation, pulmonary function, diaphragm, respiratory muscles, amyotrophic lateral sclerosis, ALS.* [Respir Care 2006;51(8):871–881.

Introduction

Amyotrophic lateral sclerosis (ALS), often referred to as Lou Gehrig's disease, is a neurodegenerative disease of the upper and lower motor neurons, resulting in muscular atrophy and spasticity.[1] It is a progressive, fatal illness with a mean survival from time of diagnosis of only 1–3 years.[2] The diaphragm and other muscles of respiration are invariably affected, and most patients die from respiratory complications. The worldwide incidence is 0.6–3.3/100,000.[3,4] The crude mortality rate is 1–2/100,000, and approximately 6/100,000 in 60–75-year-olds. Approximately 5% of cases are familial, some of which are caused by defects in the gene coding for copper-zinc superoxide dismutase, but the remainder of ALS cases are sporadic and idiopathic.[5] The median age of onset is approximately 66 years, and the male-to-female ratio is 1.6:1.[6] Because ALS often presents with insidious weakness, frequently of the limbs, there is often a lengthy delay from onset to diagnosis. One study of ALS in Southern Italy reported that the mean duration from symptom onset to diagnosis was 598.12 ± 84.26 days.[7]

ALS usually begins in one muscle group and spreads to involve others. It can involve all skeletal muscles, though ocular muscles and continence are usually preserved. There is no reliable method to predict when respiratory muscle weakness will occur, and a small percentage of patients with ALS initially present with only respiratory muscle involvement.[8,9] Because all patients eventually develop respiratory muscle impairment and most patients die from respiratory failure or pneumonia related to respiratory mus-

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cle weakness,[10] pulmonary issues are particularly important in ALS.

In 1999 the American Academy of Neurology published its evidence-based practice parameters for ALS.[11] The evidence report graded evidence as grade I, II, or III, with I being the strongest evidence. Of 23 studies cited in the respiratory-management section of the report, none were considered grade I, and the majority of studies were grade III. Another study from 1999 sought to determine the amount of variability in pulmonary care of ALS patients.[12] The authors sent questionnaires to the directors of the 48 multidisciplinary ALS centers sponsored by the Muscular Dystrophy Association and the ALS Association. Twenty centers (42%) responded and provided information on 2,357 patients. The mean interval for routine follow-up of patients was 3 months, with a range of 2–6 months. Only 25% of centers had routine pulmonary evaluations, and in 10% a pulmonologist was never consulted. Eighty-five percent of the centers routinely followed spirometry, 15% routinely used arterial blood gas values, and 10% used sleep studies or maximum inspiratory pressure (P_{Imax}). Four centers (20%) had protocols to initiate noninvasive ventilation, but there was wide practice variation regarding the time to initiate ventilatory support. Despite the lack of definitive evidence showing effectiveness, most centers used noninvasive positive-pressure ventilation (NPPV), and some also used intermittent positive-pressure breathing machines or continuous positive airway pressure. The survey showed that among major United States ALS centers there was little consensus on pulmonary care.

The literature on respiratory care in ALS has grown rapidly since 1999, and I think there is now more widespread agreement on the importance of pulmonary evaluation in ALS. Additionally, the evidence on appropriate respiratory interventions has grown. This article will review the literature on the respiratory evaluation and treatment of patients with ALS. It will also discuss other issues related to the care of patients with ALS, including end-of-life care.

Pulmonary Evaluation

Variability in disease progression can impact whether patients with ALS have prominent respiratory symptoms. Patients with slowly progressive disease and patients who develop severe limb weakness prior to respiratory muscle weakness may have few pulmonary complaints. Nevertheless, it is common for patients to complain of dyspnea with exertion and orthopnea. Patients may have nocturnal hypoventilation before the onset of any diurnal problems. This can lead to fragmented sleep. Patients may report difficulty sleeping and frequent nocturnal awakenings, which they may not attribute to respiratory difficulties. Occasionally patients will have morning headaches from hypercapnia. Clinicians should maintain a high degree of suspicion, to elicit respiratory complaints. Weak cough, chest congestion, and difficulty clearing secretions are common symptoms caused by expiratory muscle weakness. Occasionally, patients with prominent bulbar involvement will develop laryngospasm, which can be terrifying and often prompts emergency-department visits. Fortunately, these laryngospasms usually resolve spontaneously after several minutes.

Respiratory symptoms are inversely correlated with pulmonary function test (PFT) results. A 1998 study with 26 patients found that patients with symptoms had lower vital capacity (VC) (52% of predicted vs 96% of predicted).[13] The mean age and duration of ALS symptoms were similar between the 2 groups. Symptomatic patients had lower transdiaphragmatic pressure (P_{di}) (as measured via sniff and magnetic stimulation test) and lower expiratory gastric pressure (measured via magnetic stimulation test). P_{aCO_2} was significantly associated with inspiratory muscle strength, and symptomatic patients had significantly higher P_{aCO_2} and lower pH.[13] Another study found that patients with dyspnea had a forced vital capacity (FVC) of 67.9% of predicted, compared to 87.9% of predicted among those without dyspnea. P_{Imax} was 41% versus 60%, and maximum expiratory pressure (P_{Emax}) was 18% versus 32%, respectively. These differences were all statistically significant.[14]

There are numerous ways to assess respiratory muscle function, and each method has advantages and disadvantages. A brief overview of the more common tests will help clarify the remainder of this review. There are specific tests of inspiratory muscle strength, expiratory muscle strength, diaphragmatic strength, and overall respiratory function. Inspiration is performed primarily by the diaphragm,[15] but is assisted by accessory muscles of respiration. Quiet expiration is passive, but abdominal muscles contract during forced expiration, such as during a cough. The most widely used test of inspiratory strength is the P_{Imax}, in which the subject inhales against an occluded airway and a pressure transducer records the maximum pressure generated. This test is noninvasive, has well-established reference values,[16] and is sensitive for excluding weakness. Unfortunately, P_{Imax} is effort-dependent and difficult for some people to perform, so intermediate and low values can be difficult to interpret.[17] The most accurate and reproducible volitional test of inspiratory strength is the P_{di} test, which is performed by inserting balloon catheters into the stomach and mid-esophagus. The pressure difference across the diaphragm is recorded while the subject makes inspiratory efforts. This can be performed as a static measure against an occluded airway, by maximal inspiration at total lung capacity, or by maximal sniffing maneuvers. The latter technique is more reproducible than

the others.[18] The main drawback to P_{di} is that it is invasive and not well tolerated by many patients.

A more recently developed test is the sniff nasal pressure test, in which a pressure transducer is inserted into one nostril and the subject makes a sniffing maneuver. This test appears to be accurate and is more reliably performed than P_{Imax} in patients with bulbar weakness. Nonvolitional tests of inspiratory strength are performed using electric or magnetic stimulation of cervical nerve roots while measuring P_{di} or mouth pressure. These tests are performed only in specialized centers, can be technically challenging, and have a great deal of overlap between normal subjects and those with muscle weakness.

The only commonly used tests of expiratory muscles are the P_{Emax} and cough peak flow. P_{Emax} is similar to P_{Imax}, except that the subject exhales (rather than inhales) against the occluded airway. P_{Emax} is noninvasive but limited in the same ways as is P_{Imax}. Cough peak flow is performed by having the patient cough into a standard peak flow meter. This can be useful for determining if the patient can generate adequate expiratory flow to clear pulmonary secretions. Spirometry is a useful measure of pulmonary function, and is by far the most frequently used measure in ALS clinics. The FVC is reduced by respiratory muscle weakness but may remain normal until weakness is pronounced. It is also nonspecific and reflects changes in the airways, muscles, chest wall, and lung parenchyma.

Kreitzer and colleagues[19] published an early study of lung function in ALS. They sought to determine the relationship between the degree of respiratory muscle weakness and distribution of respiratory muscle weakness (ie, diaphragmatic vs more global weakness) and how these factors relate to lung volumes. The 32 patients tested had normal total lung capacity (mean ± SD 97.7 ± 14.1% of predicted), elevated residual volume (RV) (171.1 ± 62.5% of predicted), and decreased VC (73.4 ± 20.9% of predicted). P_{Emax} was significantly lower than P_{Imax} (36.9 ± 15.5% of predicted vs 61.6 ± 31.3% of predicted). The authors concluded that total lung capacity is preserved, despite decreased P_{Imax} to approximately 62% of predicted. Expiratory muscle weakness appears to be the primary determinant of RV in these patients.

To characterize pulmonary function in ALS, Fallat and colleagues[20] studied 218 patients at baseline and followed serial studies in 103 patients. The baseline measures revealed that patients had relatively normal FVC, total lung capacity, and diffusing capacity (80–103% of predicted) but that maximum voluntary ventilation and RV were more abnormal (67% of predicted and 138% of predicted, respectively). Arterial blood gas values were measured in the 30 patients who had the lowest maximum voluntary ventilation. Only one patient had an elevated P_{aCO_2} (52 mm Hg). Of the patients who had serial studies, the authors divided them into 2 groups: those who were alive at the end of follow-up and those who had died. Survivors had significantly different slopes in FVC, maximum voluntary ventilation, and RV than did patients who died during the study. FVC and maximum voluntary ventilation correlated better with time-to-death than did Norris score, which is an ALS-specific severity score ($r = 0.4$ vs 0.18). The FVC-versus-time curves had a great deal of interpatient heterogeneity and suggested a curvilinear pattern with a steeper slope as death approached. Many of the patients did not develop respiratory symptoms until their PFT values were markedly abnormal.

Schiffman and Belsh studied serial lung function in ALS patients over a 10-year period.[21] The baseline FVC was reduced to 72% of predicted, and the P_{Imax} and P_{Emax} were also abnormal. Despite PFT abnormalities, only 19% of patients had respiratory symptoms at diagnosis. The patients with respiratory symptoms had a mean FVC of 56% of predicted, compared to 76% for those without symptoms. The P_{Imax} and P_{Emax} were similar for patients with and without symptoms. VC was negatively associated with the stage of ALS. Decline in lung function was similar for each clinical stage of ALS. The average rate of decline in VC for all patients was −3.5 ± 3.4% of predicted per month. In the patients followed until death, the median survival from diagnosis was approximately 12 months. The VC decline had a great deal of interpatient variability, with a generally linear decline in FVC (Fig. 1).

It has long been established that in healthy individuals VC is generally lower in the supine position than in the seated position. The difference between upright and supine VC is greater in patients with diaphragmatic weakness. Supine FVC correlates very well with diaphragm strength, as measured by P_{di} ($r^2 = 0.76$, $p < 0.001$).[22] I have observed that supine spirometry has become a relatively common clinical measure in many ALS clinics.

A newer measure of inspiratory muscle strength is the sniff nasal pressure test.[23] In an initial study of 16 patients with ALS, FVC was normal at enrollment, but sniff nasal pressure test, P_{Imax}, and P_{Emax} were all reduced to 59–69% of predicted. All the patients were able to perform the FVC maneuver at all visits. Sniff nasal pressure test was missing 3 times with one patient, due to nasal congestion, whereas P_{Imax} and P_{Emax} were missing on 19 and 26 occasions, respectively. Patients with mouth weakness found the P_{Imax} and P_{Emax} tests difficult to perform. This study demonstrated that sniff nasal pressure test is obtainable in patients with ALS. It detects respiratory muscle weakness earlier than does FVC and it avoids some of the problems inherent in P_{Imax} and P_{Emax}. More patients who were in advanced stages of ALS were able to perform the sniff nasal pressure test than the P_{Imax} or P_{Emax} tests.

A subsequent study confirmed the value of the sniff nasal pressure test in ALS.[24] The sniff test correlates very closely with P_{di} ($r^2 = 0.6445$, $p < 0.001$) and can be

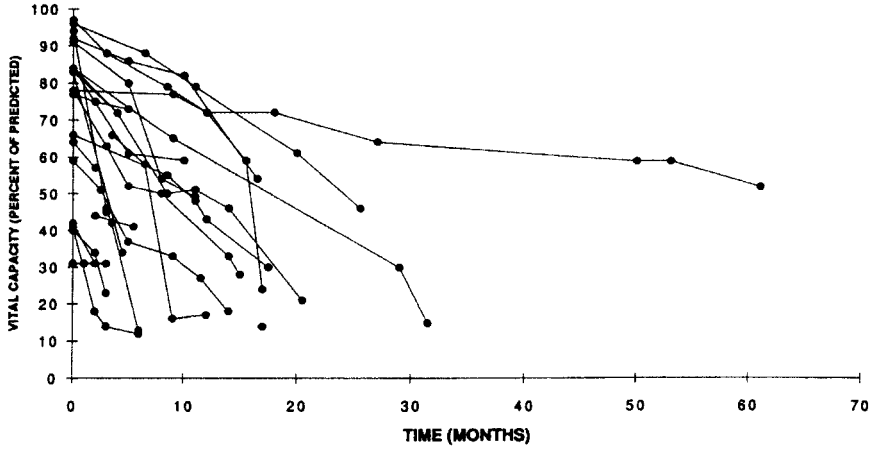

Fig. 1. Longitudinal change in vital capacity in a series of patients with amyotrophic lateral sclerosis, followed up to 5 years. The decline in vital capacity tends to be linear, but there is a great deal of interpatient variability in the rate of decline. (From Reference 21, with permission.)

obtained in more patients with advanced disease than can FVC or P_{Imax}. Additionally, sniff nasal pressure test $< 40\%$ of predicted is a significant predictor of nocturnal hypoxemia and mortality.

Other pulmonary-function measures also predict nocturnal hypoxemia and survival in ALS. Schmidt and colleagues evaluated baseline PFT values from 95 patients with ALS and followed them for approximately 1 year.[25] Single values of supine FVC, upright FVC, P_{Imax}, and P_{Emax} were all significantly associated with survival. Normal values for supine FVC, P_{Imax} and P_{Emax} were highly predictive for 1-year survival. This information is particularly useful for planning clinical trials. Many ALS clinical trials use 12 months of follow up. When establishing sample-size goals and determining enrollment criteria, it is important to be able to estimate survival in the study population.

P_{Imax} also predicts nocturnal desaturation,[26,27] though the impact of nocturnal hypoventilation and sleep-disordered breathing in ALS is not entirely clear. Gay and colleagues reported on polysomnography in 21 patients with ALS.[26] The group had fairly mild pulmonary involvement, with a mean FVC of 82% of predicted. Thirteen patients reported difficulty sleeping or being tired during the daytime. These 2 questions were 100% sensitive for predicting nocturnal desaturation, but had low specificity. Despite having preserved FVCs, 16 of the 21 patients had nocturnal-oxygen-saturation nadirs below 89%. This was predicted only by an abnormal P_{Imax}. In that study, nocturnal desaturation did not correlate with survival.

Another evaluation of sleep in ALS studied 17 patients with a mean FVC of 81% of predicted.[28] The ALS patients had more sleep symptoms than did the control group. The Stanford Sleepiness Scale score was 2.7 ± 1.4 in those with ALS, versus 0.7 ± 1.7 in the control group. The patients with ALS had 19.4 arousals per hour, and primarily nonobstructive hypoventilation concentrated in the rapid-eye-movement (REM) phase of sleep. Sleep-disordered breathing is more common during REM sleep, because muscle tone in the accessory muscles of respiration is lost during REM. As an adaptive mechanism, some ALS patients decrease their time in REM sleep, whereas others seem to preserve contraction of the sternocleidomastoid muscles during REM.[29] The small body of literature on sleep in ALS indicates that sleep-related symptoms and daytime fatigue are common. Other than P_{Imax}, most pulmonary-function measures are not predictive of sleep-disordered breathing. Lastly, patients with ALS frequently have nocturnal desaturation, and it is usually due to hypoventilation rather than to obstructive events.

Though patients may hypoventilate at night, daytime hypercapnia tends to occur late in the disease course, but is difficult to predict. Additionally, the implications of diurnal hypercapnia are not entirely clear. The ambiguities are in part related to the lack of large prospective studies of P_{aCO_2} in patients with ALS. Lyall and colleagues evaluated 81 patients with ALS in a study to evaluate predictors of hypercapnia.[30] In their study, the mean P_{CO_2} was 41.7 mm Hg, and approximately 18% of subjects had hypercapnia. In patients with substantial bulbar involvement, no noninvasive measure of respiratory muscle function was predictive of hypercapnia, whereas in patients without substantial bulbar involvement, sniff nasal pressure test was 81% sensitive and 85% specific. A smaller study of pulmonary function in patients with ALS did not find a significant association between P_{CO_2} and sniff P_{di}.[22] Additionally, a longitudinal study of 95 patients with ALS did not find a significant association between P_{CO_2} and survival.[25]

It is my opinion that P_{CO_2} is highly variable in ALS. In general, hypercapnia does not develop until there is advanced respiratory muscle weakness, but some patients will have hypercapnia unexpectedly. At times this is due to superimposed obstructive lung disease, but it can also be due to nocturnal hypoventilation. It is difficult to establish stringent rules regarding measurement of P_{CO_2} levels in ALS. It is reasonable to measure P_{CO_2} if the PFT values do not explain the patient's symptoms or if the patient has symptoms of sleep difficulties. Data are needed regarding capnography in patients with neuromuscular diseases. If a noninvasive measure of P_{CO_2} is accurate, this could allow earlier detection of respiratory compromise in ALS.

Treatment

Ventilatory Insufficiency/Noninvasive Ventilation

The most common treatment for chronic hypoventilation in ALS is NPPV. In the past, negative-pressure ventilators, such as iron lungs, cuirass ventilators, and ponchos were occasionally used, but these tend to worsen upper-airway collapse and are also cumbersome, so they will not be discussed further here.

NPPV can be delivered with either a pressure-limited or volume-limited ventilator. The most common pressure-limited ventilators are bi-level units, with which both an inspiratory and an expiratory pressure are set. Most commonly used units allow the operator to enter a backup respiratory rate, which is important, because many ALS patients have a component of central hypoventilation. Many newer ventilators can operate in several different ventilation modes and can provide inspiratory pressure up to 30 cm H_2O. There are several manufacturers and models available, but typical bi-level positive-pressure ventilators are small enough to fit on the back of a wheelchair and can be adapted to operate from a battery or in an automobile (Fig. 2). Volume-limited ventilators are adjusted based on a goal tidal volume rather than an inspiratory pressure needed to achieve that volume. Most volume-limited ventilators have been designed for long-term invasive ventilation through a tracheostomy tube, so they are equipped with a full set of alarms and backup systems. Volume ventilators also tend to be larger and heavier than bi-level-pressure ventilators, but they can still be attached to a motorized wheelchair and operated from a battery. Some practitioners believe that volume ventilators provide more ventilatory support than pressure-limited ventilators and they prefer to use them for patients with advanced disease. However, newer bi-level units can provide inspiratory pressure high enough to provide full support for most patients.

There are many different noninvasive-ventilation interfaces; nasal masks are the most common (see Fig. 2).

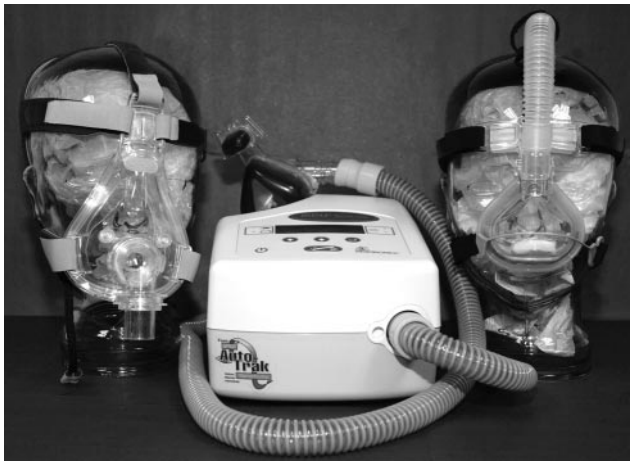

Fig. 2. Two noninvasive-ventilation interfaces and a bi-level positive-pressure ventilator.

These masks are typically triangular, have a soft rubber seal, and are held in place with straps or other headgear.

Another popular NPPV interface is "nasal pillows" (also known as nasal pads or an Adams circuit). This type of mask has 2 pieces; one fits into each nostril. Many patients do well with a nasal mask, but some patients who have mouth weakness have difficulty preventing air leakage through the mouth. Sometimes a chin strap can prevent air leakage, but at times a full face mask is needed. Some patients prefer to use a mouthpiece rather than a mask during the day. This allows the patient to speak and eat while using the ventilator as needed throughout the day.

Table 1 summarizes studies of the impact of NPPV on survival in subjects with ALS. Pinto and colleagues were the first to compare NPPV with standard care in patients with ALS.[31] They investigated the effect of NPPV on survival in 18 patients. The 2 groups did not differ significantly at baseline, except for lower VC and lower P_{aO_2} in the NPPV group. Three-year survival was significantly higher in the NPPV group (87.5% vs 22.2%, $p < 0.004$). One-year survival from the onset of gas-exchange abnormalities was also significantly higher in the NPPV group (74.1% vs 0%, $p < 0.001$).

Two years after the study by Pinto et al, Aboussouan and colleagues stated that "NPPV was the treatment of choice for respiratory failure in neuromuscular diseases, and a randomized trial would not be ethically allowable." Based on that assertion, they undertook an observational study of NPPV in ALS patients.[32] They sought to determine if patients who tolerate NPPV have better survival and whether patients with bulbar symptoms are intolerant of NPPV. Patients were offered NPPV if they developed orthopnea or hypercapnia ($P_{aCO_2} > 45$ mm Hg). Thirty-nine patients met their criteria to use NPPV, and 18 patients tolerated NPPV. The patients who tolerated NPPV had a higher mean FVC and fewer bulbar symptoms at the

Table 1. Summary of Controlled Studies of Noninvasive Positive-Pressure Ventilation on Survival in Amyotrophic Lateral Sclerosis

First Author, Year	Study Design	Participants and Treatments	Findings
Pinto[31] 1995	Nonrandomized, controlled	9 NPPV 9 standard care	3-year survival higher with NPPV (87.5% vs 22.2%, $p < 0.004$)
Aboussouan[32] 1997	Observational	39 NPPV 18 intolerant of NPPV	Relative risk of death = 1.7 if intolerant of NPPV
Kleopa[33] 1999	Observational	38 NPPV > 4h/d 32 NPPV < 4h/d 52 refused NPPV	Mean survival 35.5 mo in NPPV users vs 29.5 mo in nonusers ($P = 0.01$)
Aboussouan[34] 2001	Observational	23 NPPV 24 intolerant of NPPV	Median survival better in NPPV users: 20 mo vs 5 mo ($p = 0.002$)
Farrero[35] 2005	Observational, comparing use of early respiratory protocol with standard care	49 in early protocol (46 used NPPV) 15 not in protocol (11 used NPPV)	Survial from diagnosis longer in early protocol group: 61 mo vs 35 mo ($p = 0.01$), when bulbar-involvement patients excluded from analysis
Bourke[36] 2006	Randomized clinical trial	22 NPPV 19 standard care	Median survival 219 d in NPPV users vs 171 d in control patients ($p = 0.006$). Most NPPV benefit in group with good bulbar function.

NPPV = noninvasive positive-pressure ventilation

time of respiratory insufficiency. The relative risk of death among the NPPV-intolerant patients was 3.1 (confidence interval 1.8–9.6), compared to the patients who tolerated NPPV. Survival curves were stratified by extent of bulbar involvement. In each stratum there was a survival advantage in the patients who tolerated NPPV (Fig. 3). In multivariate analysis, adjusting for bulbar symptoms, use of neuroprotective medications, and P_{Emax}, the relative risk of death among the NPPV-intolerant patients was 1.72 (confidence interval 1.03–3.03).

Kleopa and colleagues[33] studied the impact of NPPV on survival and whether NPPV alters the decline in pulmonary function in ALS. NPPV was offered when FVC fell below 50% of predicted, if the patient had symptoms of respiratory insufficiency, or if FVC fell more than 15% in a 3-month period. Patients were divided into 3 groups: group 1 used NPPV for more than 4 h/d, group 2 did not tolerate NPPV well and used it less than 4 h/d, and group 3 refused to try NPPV. The study included 122 patients. Survival from the time of diagnosis and from the time of NPPV initiation was significantly longer in group 1 than in group 3. Survival from the time NPPV was offered was 14.2 ± 13.0 months in group 1, and 4.6 ± 12.0 months in group 3. The slope of decline in pulmonary function was similar for the 3 groups prior to starting NPPV, but following NPPV group 3 had a significantly faster decline in FVC than did group 1. This study raises the possibility that NPPV may alter the disease course of ALS. If this is true, ALS patients should be encouraged to use NPPV prior to the onset of respiratory insufficiency.

The NPPV studies described thus far were all observational, meaning that patients were not assigned to use NPPV as part of a study intervention. Because there is such great interpatient heterogeneity in the rate of progression of ALS, observational studies are fraught with problems. The biggest concern with these studies is that there is selection bias, because the patients who tolerate NPPV and use it successfully may tend to be those with more slowly progressing disease. If this was true in the various NPPV studies, then NPPV would appear to prolong survival even if survival differences were simply due to underlying disease differences. To overcome selection bias, a randomized trial was necessary. This year, Bourke and colleagues published their findings on the first randomized trial of NPPV in ALS.[36] They randomized patients to NPPV at the time of orthopnea with $P_{Imax} < 60\%$ of predicted or symptomatic daytime hypercapnia. Twenty subjects were assigned to NPPV and 19 to standard care. The 2 groups were similar at the time of randomization with respect to age, gender, disease duration, bulbar score, and lung function. Survival among all patients was significantly longer in the NPPV arm (219 d) than in the standard-care arm (171 d, $p = 0.006$). The authors also analyzed survival in patients who had good bulbar function versus those who had poor bulbar function. NPPV's effect on survival was significant only in the subjects who had good bulbar function (216 d vs 11 d, $p = 0.006$). This study confirms the findings of the earlier observational studies. Though no survival benefit was seen in patients with poor bulbar func-

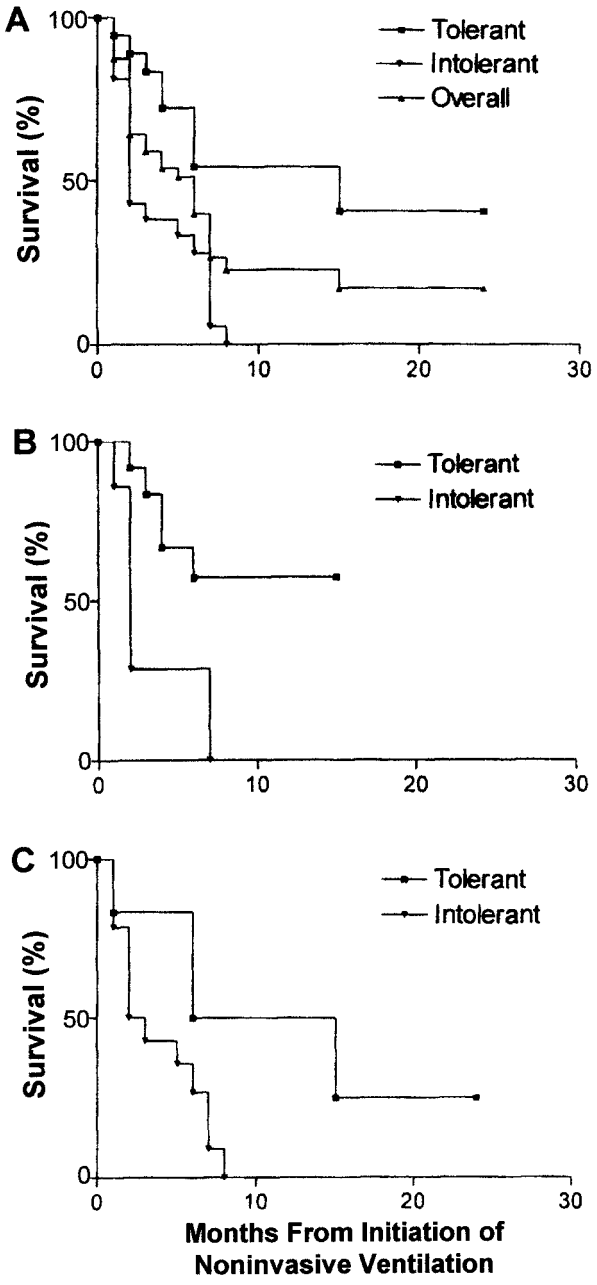

Fig. 3. Survival curves from the initiation of noninvasive positive-pressure ventilation (NPPV), comparing patients who tolerated NPPV, patients who did tolerate NPPV, and overall survival. A: All patients, among whom the relative risk of death in intolerant (versus tolerant) subjects was 3.1 ($p < 0.001$). B: Patients with mild or no bulbar involvement, among whom the relative risk of death in intolerant (versus tolerant) subjects was 3.5 ($p = 0.01$). C: Subjects with severe bulbar symptoms, among whom the relative risk of death in intolerant (versus tolerant) subjects was 2.7 ($p = 0.03$). (From Reference 32, with permission.)

tion, the subgroups were small and the study was underpowered to detect survival differences.

As a number of studies indicated that NPPV could improve survival in ALS, concern began to surface that NPPV would simply lead to prolonged suffering. But a number of studies have refuted that concern and indicated that NPPV can also improve quality of life, sleep symptoms, and cognitive function. Aboussouan and colleagues evaluated respiratory quality of life, using the Chronic Respiratory Questionnaire, in patients before and after using NPPV.[34] They found that, over time, dyspnea score showed a trend toward worsening but that NPPV significantly improved fatigue score, from 11.1 to 14.9 ($p = 0.03$).

Another study followed 30 patients with ALS treated with NPPV for up to 34 months.[37] There were improvements in multiple respiratory symptoms and quality-of-life measures for the first 10 months of NPPV use. A similar study with 16 patients treated with NPPV found significant improvements in the "vitality" domain of the Medical Outcomes Study 36-question short form, despite disease progression. Some patients had sustained improvements in quality of life for up to 15 months.[38]

In another study, 9 ALS patients with hypoventilation and cognitive impairment were compared to 10 ALS patients without hypoventilation.[39] The patients were treated with NPPV for 6 weeks, and they had significant improvements in the Kendrick Object Learning Test, list learning, and list recall.

The randomized trial of NPPV discussed above used quality-of-life changes as the primary outcome measures.[36] That study confirmed the results of earlier observational studies. Patients treated with NPPV maintained the mental component score on the Medical Outcomes Study 36-question short form and the sleep apnea quality-of-life symptoms domain above 75% of baseline significantly longer than did the control group. The NPPV group also had improvements in the time-weighted values for the 2 quality-of-life measures.

Though there are still limitations with the studies of NPPV in patients with ALS, the available evidence is consistent and repeatedly shows that NPPV can improve respiratory symptoms, sleep symptoms, cognitive function, and survival. At present it should be considered the standard of care to offer NPPV to ALS patients who have respiratory symptoms and evidence of respiratory muscle weakness. The strongest evidence suggests using hypercapnia or a P_{Imax} below 60% of predicted as the criteria to start NPPV, but more studies are needed to determine if it is beneficial to initiate NPPV earlier in the course of the disease or based on other criteria.

Invasive Ventilation

Patients frequently do well with NPPV for prolonged periods, despite disease progression. As respiratory muscle weakness progresses, these patients usually need to increase both the level of ventilatory support and the duration of ventilator use. It is not uncommon for patients to

progress to needing NPPV nearly 24 hours per day. There are several factors that limit the effectiveness of NPPV. Some patients simply cannot tolerate the sensation of a face mask or the airflow in the nose or pharynx. Though this is uncommon, it occurs more frequently in patients with bulbar disease.[40,41] If the patient can tolerate NPPV, it is usually effective until the patient develops severe problems with secretions and inability to cough. Though noninvasive secretion-clearance methods will be discussed below, these eventually become ineffective when bulbar involvement is severe. In the United States, less than 10% of ALS patients use invasive mechanical ventilation through a tracheostomy tube, but this can provide long-term respiratory support in patients who cannot tolerate NPPV.

Invasive ventilation use is limited by its cost, the need for 24-hour caregivers, and the concern that it will prolong life beyond the point that the patient can communicate or interact with others. Moss and colleagues studied patients receiving home mechanical ventilation, to learn about the "outcomes, benefits, and burdens" of this controversial treatment. They sought to determine the prevalence of mechanical ventilation and the appropriateness of home ventilation in the patients receiving it.[42] Twenty-four ALS patients on home ventilation were identified. Approximately 80% of those patients did not decide on mechanical ventilation until an emergency arose. Despite this, about 90% of the patients and 94% of the caregivers were happy with the choice. Nearly identical results were found in 2 subsequent studies of ALS patients on invasive ventilation.[43,44] It is evident that in the United States few patients with ALS choose invasive mechanical ventilation, but those who opt for tracheostomy do not regret the decision and can be supported for a number of years. Death in patients with tracheostomy comes either from a decision to withdraw ventilatory support or from complications unrelated to respiratory status, such as infection.

Prevention of Infection and Clearance of Airway Secretions

Respiratory infections are a common concern and a relatively frequent complication of ALS. Immobility, weakened cough, hypersialorrhea, and impaired swallowing all contribute to an increased risk of pulmonary infection. Though few data exist on the subject, there are several common-sense approaches to infection prevention that should be implemented. Patients should routinely be vaccinated against *Streptococcus pneumoniae* and influenza. Patients should also be educated about aspiration. They should be taught to change the consistency of their foods and to use a chin tuck when swallowing if they begin to notice aspiration while eating.[45]

A patient's ability to cough effectively can be evaluated by measuring the cough peak flow. This is accomplished using a standard peak flow meter adapted to an anesthesia face mask. A cough peak flow $>$ 160 L/min is necessary to clear airway debris. Because cough peak flow decreases during acute illness, it has been suggested that once a patient's cough peak flow is $<$ 3 L/s, he or she is at risk for impaired airway clearance. This threshold is an appropriate time to implement assisted cough techniques. Though there are various manual methods to assist cough, they can be challenging for wheelchair-bound individuals, and they do not generate cough flows as high as those obtained using a mechanical in-exsufflator.[46] Bach reported a series of patients with ALS who had relatively few respiratory complications over a period of years when they adhered to a regimen of mechanically assisted cough, noninvasive ventilation, and pulse-oximetry monitoring.[47]

Another more recently evaluated airway-clearance technique for patients with ALS is high-frequency chest-wall oscillation (HFCWO). This technique generates high flow in small airways and is thought to mobilize secretions from the distal airways to the larger airways, where they are more easily cleared. HFCWO can be delivered with a commercially available vest that inflates with air and vibrates rapidly. A multicenter randomized study of HFCWO in ALS has been reported in abstract form.[48] In that study, 46 patients were followed for 12 weeks. HFCWO appeared to be well tolerated. Compared to those who did not use HFCWO, the HFCWO users had less breathlessness ($p = 0.021$) and coughed more at night ($p = 0.048$), possibly indicating that the intervention succeeded in loosening airway secretions.

As stated previously, there is a great deal of variability in ALS evaluation and treatment. Additionally, the literature leaves many questions unanswered with respect to the optimal manner to initiate and use NPPV. Figure 4 shows an algorithm that reflects my approach to evaluating and treating patients with ALS.[49]

Nonpulmonary Issues

As noted above, swallowing difficulties invariably develop with ALS. This complicates pulmonary care and also places the patient at risk for dehydration and malnutrition, which can accelerate decline in muscle strength. Early placement of a gastrostomy tube and nutritional supplementation can improve survival in ALS.[50] Additionally, peri-procedure complications are more common if the gastrostomy tube is inserted too late in the disease course,[51] so the ALS practice parameter recommends early placement of a gastrostomy tube.[11]

Though respiratory issues are common and troubling in ALS, these patients confront a number of other challenges, including difficulties with mobility and speech. It is crucial that the patient have access to a multidisciplinary team that includes nurses, speech therapists, occupational ther-

Fig. 4. A proposed respiratory evaluation and treatment algorithm for patients with amyotrophic lateral sclerosis. FVC = forced vital capacity. P_{Imax} = maximum inspiratory pressure. NPPV = noninvasive positive-pressure ventilation. Modified from Reference 49, with permission.

apists, and physical therapists. These experts can address communication devices, which can range from simple letter boards to computer speech synthesizers with optical controls. Patients benefit greatly from orthotic devices, mechanical wheelchairs, and lifts. Physical therapists can prescribe exercises to maintain range-of-motion and prevent contractures. Lastly, discussions regarding end-of-life care should take place relatively early in the course of ALS. Patients need to be educated about the various ventilator options and encouraged to make their wishes known to loved ones and clinicians. Regardless of the patient's ventilator choices, attention needs to be given to optimizing quality of life and avoiding suffering in the later stages of ALS. Patients and caregivers should have access to support groups, and hospice programs should be readily endorsed. Hospice programs are excellent at providing appropriate palliative care and should be engaged by most patients with ALS.

Summary and Future Directions

Knowledge about respiratory issues in ALS has grown dramatically over the last 10 years. Advances in the pul-

monary care of ALS patients have allowed patients to live longer lives while alleviating shortness of breath and improving overall well-being. ALS is an idiopathic fatal disease, but, fortunately, there is extensive research underway on the pathogenesis of ALS and there might be a cure in the future. A promising recent study with a mouse model of ALS found that viral vectors can be injected into peripheral muscles to transport growth factors to the central nervous system, which dramatically improved survival.[52] And a surgeon with extensive experience using diaphragmatic pacing in patients with spinal-cord injury has turned his attention to ALS, and he recently reported on his promising initial experiences.[53]

Until a cure is found for ALS, respiratory care providers have a crucial role in evaluating, educating, and treating patients. Respiratory interventions have a greater impact on survival and quality of life than any other ALS treatments.

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Discussion

Hess: How do you select the BiPAP settings for these patients? Do you do that empirically? Do you do overnight oximetry? When do you send them to the sleep laboratory? What kind of settings do these patients end up on?

Lechtzin: That's a great question, and I think my practice probably differs from many others. I tend to do it empirically.

Hess: That's what I do, too.

Lechtzin: In the recent trial by Bourke et al,[1] almost all the patients had BiPAP started in the hospital after a sleep study. Charlie Wiener, my mentor in this subject, who was seeing these patients before I was, initially tried to get sleep studies on everybody, but found that the sleep laboratory was too busy, didn't have the interest, and wasn't well equipped for dealing with fairly debilitated patients. It just wasn't practical. So I start them empirically. I tend to start on fairly low settings, such as an inspiratory pressure of 8 cm H_2O and an expiratory pressure of 4 cm H_2O, and see how they do. Then I titrate settings based on symptoms. Patients may say, "I had orthopnea and now I can lie flat." I say, "Hey, I think we're doing pretty well." If they say, "I feel like I'm getting blasted away," we turn down the settings.

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Benditt: I've also observed that with a lot of neuromuscular diseases the sleep laboratory is not able to handle them. And because most of these diseases are progressive, getting somebody with ALS into the laboratory every 6 months is impossible, so we've given the home-care providers very wide ranges that they can use for setting the BiPAP at home. And we start with low settings, like you do, then, with symptoms, and sometimes with oximetry, we'll increase the support.

Hess: We do the same thing. I'm encouraged to hear that's what others are doing.

Lechtzin: I'm trying to do more capnography in clinic, but I have yet to decide whether it's going to be helpful. Patients, by and large, don't want to have serial blood gases done. I

haven't found that it really changes my practice much. And having a group of home-care providers that I'm familiar with and who are familiar with ALS patients has been key, although I'm not always able to find those providers, and, depending on the patient's insurance, they sometimes are limited in who they can use.

Hill: I'd like to expand on the sleep-laboratory issue, generalizing the comments to neuromuscular disease patients in general. If you ask people who want to titrate noninvasive ventilation in sleep laboratories what it is they do, they usually tell you, "Well, you know, the usual. The apneas and respiratory events." And they come up with some home-cooked formula for doing so, but the end points we're looking at, once patients leave the laboratory, are entirely different.

For my neuromuscular patients, I follow gas-exchange end points. I follow occasional blood gases or nocturnal oximetry, although in the ALS patients I tend to be less invasive. These are patients who don't want much done a lot of the time. They don't want to spend time in a sleep laboratory. And I've had the experience of having a sleep laboratory tell me, "This patient needs to be on pressures of 11 cmH_2O inspiratory and 8 cmH_2O expiratory", because these were the pressures that eliminated respiratory events. But a pressure support of 3 cmH_2O is very unlikely to reverse nocturnal hypoventilation. My view is that we don't really know how to use the sleep laboratory to titrate noninvasive ventilation pressures in patients with chronic respiratory failure.

Lechtzin: I have seen a few protocols that some neurologists have developed, for ALS in particular, that seem to make sense. But I agree: when I've sent my patients to our sleep laboratory they wind up with settings typical for sleep apnea, and that's not what these patients need.

Deem: Regarding the cost that you mentioned for invasive mechanical ventilation. How are those costs generated? And are they true *costs*, or *charges*? And how does noninvasive ventilation compare, in terms of yearly cost?

Lechtzin: I should defer to Josh Benditt on this. My recollection is that those were patient out-of-pocket expenses, rather than actual costs. A lot of it comes down to nursing care. Patients on home ventilation should generally have 24-hour care. Often that falls on families, but families often aren't available to provide care 24 hours a day. And so it often comes down to unskilled nursing, and nursing techs, and various other personnel who aren't covered by insurance.

Benditt: That's absolutely correct. It's almost all care, and the issue is that, in the United States, Medicare and other insurers will cover the equipment, such as ventilators and catheters, but the attendant care is labeled "custodial" care, and they will not pay for that. And that is the thing that gets you up over the $150,000, and not only is it costly, it's very hard to find providers, and so families end up training many of their own home-care providers. It differs from state to state, but in some places you have to have certain qualifications to be a respiratory home-care provider, and that makes it even more expensive, and it's not covered. Although this hasn't been well studied, I suspect the reason that, in the United States, the percentage of patients going onto long-term is only 5%, is in part economic.

Jubran: When do you start noninvasive ventilation in patients with neuromuscular disease? You said that the earlier you start noninvasive ventilation, the better these patients may do. Some people are recommending a forced vital capacity of less than 50% of predicted. What's your criterion?

Lechtzin: It's probably a moving target, and it depends on the patient. Some patients who are well past the time that I think they should start say, "No, no. I don't want another piece of equipment in my home." There are others who have perfectly normal lung function and say, "I want everything you have to offer." I try to strike a balance, but I often look for indications to start noninvasive ventilation earlier.

At baseline I'll typically measure the upright and supine vital capacity, and if supine vital capacity is below 50% of predicted, I'll use that as a criterion. If the maximum inspiratory pressure is low, I'll use that. If they have an elevated P_{CO_2}, I'll use that. At times I've measured transdiaphragmatic pressure, and argued with insurance companies, saying, "This is a measure we ought to use." It's something that's not well established. Clearly, when patients have fairly profound diaphragm weakness, they ought to be on noninvasive ventilation, but how early we ought to start is still not clear.

Panitch: I am largely an empiricist when it comes to settings for children with neuromuscular disease, and I've spoken to pediatric colleagues who have had similar frustrations in sleep laboratories. And in children, sleep-laboratory studies are even less common than in adults, so it's harder to get them into a sleep laboratory. But I think we often observe abdominal asynchrony, and that's interpreted as upper-airway obstruction, and someone says, "I've got to get rid of this," so they keep cranking up the end-expiratory pressure and we end up with very high end-expiratory pressure. And, because we're soft-hearted pediatricians, we don't use esophageal catheters very frequently, but I think it's pretty clear that upper-airway obstruction is *not* the mechanism of asynchrony.

Brown: What are the proposed mechanisms for the improved survival associated with early noninvasive ventilation?

Lechtzin: I can certainly speculate. Clearly, when somebody has respiratory-muscle weakness, desaturation, and hypercapnic failure, it makes sense that a ventilator would help them live longer. Patients with ALS and respiratory muscle weakness, even if it's fairly mild, have decreased lung compliance, and positive-pressure ventilation might counteract that impairment in lung compliance and decrease the work of breathing. Acidosis or hypercapnia impair muscle function, so treating that might improve muscle function. And certainly respiratory-muscle fatigue is possible. These patients might be working very close to their maximum diaphragm pressure and developing fatigue, so if you can rest them, even at night, perhaps you'll improve diaphragm function during the day. But these are only speculations.

Brown: It seems that all those things would happen, but why does it improve survival? What if you do it now, or 6 months from now, and you catch them with a high P_{CO_2}, and you reverse it with noninvasive or invasive ventilation? It's perplexing to me.

Lechtzin: The other issue is getting patients to learn to use and get used to noninvasive ventilation. There's often a delay in getting the equipment to their house, and a delay in working out all the problems with the equipment, and a delay in having the patient get used to it. Certainly, if you start them early, you can work out those kinks, and so they may be getting more benefit from it at an earlier point.

Hill: In Bourke's randomized controlled trial,[1] how did they get around the ethical problem? I would have considered noninvasive ventilation the standard of care in patients whose FVC is less than 50% of predicted, and about half of their patients had that. How did they get around that problem?

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Lechtzin: That's a great point, and if you look at the *Annals* study from 1997, which was an observational study, the authors say in their introduction, "We couldn't do a randomized trial because it's unethical."[1] That was 9 years earlier. Bourke et al looked at the practice patterns in England, and, up until recently, very few people were using noninvasive ventilation in England, so they thought it was justifiable. It wasn't the standard of care there.

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Brown: So, say I'm 64 years old. Would you recommend I start noninvasive ventilation? Before it's too late?

Mehta: My question has to do with that. In Canada we don't have to consider whether patients can afford certain therapies. How much does that issue come into play in the United States? Second, respiratory failure is an ultimate eventuality in these patients, and you said that 90% of them actually decided at the time of respiratory failure to be ventilated. Do you start to have discussions with these people early on about respiratory failure? It would be great to start early, prepare them, educate them, show them what life would be like with noninvasive or invasive ventilation.

Lechtzin: I hope I am doing a better job than that study in which 90% hadn't made a decision in advance. I try to bring it up early on, sometimes the first time I meet the patient, depending on where in the spectrum of disease they fall. And I certainly try to address it at each visit, to find out their feelings, and to teach them about the different options. It's difficult to know how much the economic factors affect this. For some people it's certainly a big factor. A lot of it is that patients don't want to feel like they're a burden to their family, and that has some role. But it is very much a cultural phenomenon that differs from place to place. For instance, in Japan I think over 60% of people with ALS go onto long-term invasive ventilation. So there are cultural factors in addition to economic factors.

Mehta: Any idea of how that compares to percentages in North America?

Lechtzin: In North America it's probably about 5%. And the Japanese think we're killing off patients.

Hess: In the patients who were getting diaphragmatic pacing, what is the extent of their bulbar disease, and is there any concern about upper-airway obstruction?

Lechtzin: My recollection is that some of them have pretty advanced bulbar involvement, and some of them don't. I don't know that any thought has been given to the concern of upper-airway obstruction, but certainly it could become a problem. There are patients who he's done the procedure on that are on both BiPAP and diaphragmatic pacing, and he has not excluded patients who are already on BiPAP when they come to him.[1]

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Brown: Back to the realm of anecdotal experience. I make it a habit to discuss the prospect of noninvasive and invasive ventilation with patients with neuromuscular and other disorders. It is not uncommon for patients to say that they don't want any part of tracheostomy and home ventilator. I dutifully record that in the medical record, and then it's almost always the case that when they show up in the emergency room with aspiration pneumonia or another respiratory problem, they change their minds. I've almost gotten to the point where I think it doesn't make sense to go through all of that, and instead should I just ask them what they want done when they come to the emergency room.

Mehta: Not just with these chronic illnesses, but with other chronic illnesses, patients will present with an aspiration pneumonia or pulmonary edema or something that we think is acutely reversible, so I don't think it's unreasonable to support them during that time. But I think it's important to have the discussion, because they'll probably progress gradually and eventually require long-term ventilation. It's important to prepare them emotionally for that event, and have a discussion about what direction to go if we can't wean them from mechanical ventilation.

Hill: I would support that. I assume that part of your comment was a little bit facetious, Bob, but clearly you need to prepare not only the patients, but their families for this. This is a family disease. And in our ALS clinic, which is multidisciplinary, the first time I see them I go through the whole thing about how their muscles are affected, what to expect, what kind of modalities we have, and I'm sure Noah and Josh do the same thing. Actually, very few of these patients end up changing their minds. If you plan well ahead, they go through the usual noninvasive ventilation, and most of them *don't* want invasive ventilation and they go on to hospice, and usually it works out as well as can be expected and hospice usually does a very good job.

With the patients who do go on to invasive mechanical ventilation, the families bear enormous emotional, psychological, and financial burdens. So it's very important that when a patient says, "Yes, I want that tracheostomy!" that the family be informed about what that means, and how they need to participate in that decision.

On another subject, I was a little befuddled by what you showed about high-frequency chest-wall oscillation, where you had less breathlessness in that group. Was that breathlessness during use, or in between?

Lechtzin: We had several visual analog scales for patients to complete, and one of the 12-week outcomes was lower breathlessness score.

Hill: Meaning just, in general, "How breathless are you?"

Lechtzin: Right.

Hill: And what does "noisy breathing" mean? Why did you ask about it? Come on: ask your wife at night!

Lechtzin: I think it was a holdover from studies in chronic obstructive pulmonary disease or cystic fibrosis, where you expect more problems with sputum production, things of that sort.

Hill: What about indices of sputum production or cough effectiveness?

Lechtzin: We looked at that and didn't see any effect. Going into it, I was very skeptical that high-frequency chest-wall oscillation was going to do a lot of good for patients whose main problem is weakness, because, even if the oscillation loosens sputum in the peripheral airways and moves it proximally, the weak patient can't cough it out.

Hill: Exactly. Regarding noisy breathing, one thing I hear repeatedly from the spouses of patients with ALS is, "He used to snore, but that went away." Any thoughts about that?

Lechtzin: Even though the studies don't suggest that obstructive sleep apnea is a big problem, upper-airway obstruction can be a problem. But if you can't generate enough inspiratory force, you might lose that.

Hill: I've always thought that was it.

Benditt: About chest-wall vibration and dyspnea, there are a lot of reflex arcs, and I think one theory about how the chest wall vibration might reduce breathlessness is that it may affect that feedback loop to the medulla. I think that's been shown in other disease processes.

Hill: But there's a carryover.

Benditt: A carryover; yes, I think there is.

Brown: What controls did you have in the study of the Vest [high-frequency chest-wall oscillation] in ALS?[1]

REFERENCE

1. Lange DJ, Lechtzin N, Davey CS, Gelinas D, Heiman-Patterson T, David W, et al. A randomized, controlled trial of high frequency chest wall oscillation in ALS. Neurology (2006, in press).

Lechtzin: All the participants had ALS, and they were randomized to either the Vest or standard care. They were given some education about assisted cough and airway clearance, but there was no control arm beyond that.

Brown: So you don't know how many coughs per day occurred?

Lechtzin: No. And we don't know how much of this is from placebo effect with the Vest. The next follow-up study would involve a sham Vest.