

CLINICAL APPROACH TO THE RESPIRATORY MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Carlayne E. Jackson, M.D.

University of Texas Health Science Center
San Antonio, TX

Case Report

A 55 y/o female with a recent diagnosis of ALS presents for her routine follow-up exam complaining of restless sleep. She reports getting up to urinate 4-5 times a night. Her primary care provider prescribed Halcion however she continues to awaken frequently. As a result, she is severely fatigued throughout the day and is having trouble concentrating at work. Her forced vital capacity is 70% of predicted. What additional tests should be performed and what can be done to improve her sleep continuity?

Non-invasive Positive Pressure Ventilation (NPPV)

1. Why should I prescribe NPPV for my ALS patients?

A study from the Cleveland Clinic demonstrated a 3.1-fold increase in the risk for death in patients with ALS who could not tolerate NPPV when compared to those who could tolerate it (1). The difference in survival persisted even after stratification for the presence or absence of moderate or severe bulbar symptoms, however bulbar patients were less tolerant of NPPV (30% tolerance vs. 46% tolerance among patients with mild or no bulbar symptoms).

A retrospective study by Kleopa et al. (2) analyzed the results of NPPV use in 122 patients followed at Hahnemann University. All patients were offered NPPV when their FVC dropped below 50% of predicted. Group 1 (n=38) used NPPV >4 hours/day, Group 2 (n=32) used NPPV <4 hours/day due to poor compliance, and Group 3 (n=52) refused NPPV. There was a statistically significant improvement in survival from initiation of NPPV in Group 1 (14.2 months) compared to Group 2 (7.0 months, p=0.002) or Group 3 (4.6 months, p<0.001). Furthermore, Group 1 had a slower mean decline in vital capacity (-3.5% change/month) compared to Group 2 (-5.9% change/month, p=0.02) and Group 3 (-8.3% change/month, p<0.001).

A cohort study of 47 patients from the Cleveland Clinic (3) compared survival and FVC% decline in tolerant (n=23) and intolerant (n=24) patients. The mean FVC% at the time of initiation of NPPV was 41% (range 16-70%), similar to the previously published studies. The median survival in intolerant patients was 5 months compared to 20

months in tolerant patients ($p=0.002$), again confirming the apparent survival benefit of NPPV. A Chronic Respiratory Index Questionnaire was also administered to 8 patients pre and post NPPV to assess the impact of NPPV on QOL and showed improvements in the fatigue ($p=0.03$) and mastery ($p=0.07$) scores. Their study, in contrast to the Kleopa paper, showed that NPPV did *not* change the rate of decline of FVC or FEV1. In addition, the mean change in FEV1 due to initiation of NPPV was -5.94% predicted points ($p=0.07$) suggesting that NPPV may actually have a deleterious effect on spirometric measurements. The authors speculate that unloading of respiratory muscles by NPPV may result in deconditioning and therefore, suggest that there is no evidence to support recommendations to initiate NPPV at an earlier timepoint. This study, however, did not have an “early” intervention group and the cohort of patients receiving NPPV was small.

Lyall et al (4) prospectively measured QOL in a cohort of 16 patients with ALS with symptomatic hypoventilation treated with NPPV using the SF-36 questionnaire, ALS Functional Rating Scale, and the Epworth Sleepiness Scale. The results were compared to 11 control patients with ALS who had normal diaphragmatic function. NPPV improved scores in the “Vitality” domain by as much as 25%, for periods of up to 15 months, despite disease progression. NPPV did not cause reduced QOL, as any fall in scores in the ventilated group were comparable to those noted in the control group. The mean Epworth Sleepiness Score in the NPPV group at baseline was 9.25 and the control group was 5. Following initiation of NPPV, the mean score fell to 4 ($p < 0.0001$). The authors concluded that NPPV enhances QOL when used to treat sleep-disordered breathing in ALS patients.

2. When should I prescribe NPPV for my ALS patients?

Although the benefits of NPPV are apparent even in these small observational and retrospective studies, there is still no consensus as to which physiologic marker and/or clinical symptom(s) should be used to trigger the initiation of NPPV. A recent evidence-based review of the subject pointed out that most patients with ALS are symptomatic of hypoventilation by the time vital capacity (FVC) falls below 50% of predicted (5). Early symptoms of respiratory insufficiency include frequent nocturnal arousals, nightmares, morning headaches, and excessive daytime sleepiness (6). Patients and/or clinicians may not initially associate these symptoms with a decrease in respiratory muscle function. A history of exertional dyspnea may not be elicited, even in the face of moderate respiratory insufficiency, since many patients have significant mobility difficulties.

The AAN ALS Practice Parameters provide a management algorithm that recommend that NPPV should probably be instituted when patients are symptomatic and when FVC reaches 50%. The Health Care Financing Administration (HCFA) has also recently established criteria (7) for initial coverage of respiratory assist devices which serves to establish a “standard of care”. In order for NPPV to be covered by Medicare, the patient must have documentation of symptoms characteristic of sleep-associated hypoventilation, such as hypersomnolence, excessive fatigue, morning headache,

cognitive dysfunction, or dyspnea. In addition, a patient must demonstrate an arterial blood gas PaCO₂ which is >45mmHg while awake, have nocturnal oximetry data demonstrating oxygen desaturation <88% for at least five continuous minutes, have FVC < 50% of predicted or a maximum inspiratory pressure < 60 cm H₂O. As a result, new software has been developed for nocturnal oximeters to detect incremental oxygen desaturations and to document the duration of each desaturation. These HCFA criteria are based on measurements corresponding with relatively severe respiratory insufficiency.

Several recent studies have documented evidence of nocturnal hypoventilation even in patients with relatively normal FVC measurements (8). As a result, there has been a recent trend to consider initiation of NPPV earlier than the current “standard of care” promoted by the HCFA criteria and AAN recommendations. There are several studies being planned to evaluate whether there is additional survival benefit in instituting NPPV earlier.

The rationale for earlier intervention with NPPV is supported by our knowledge of sleep physiology. Hypoventilation due to diaphragmatic weakness leads to decreased REM sleep, hypopneas, oxygen desaturations, and hypercapnia (9). Arousal is the defense against hypoventilation, but results in sleep fragmentation. These events lead to a cascade of problems: further depression of arousal, depression of chemoreceptors causing hypoventilation to progress, neurohormonal changes, pulmonary hypertension, arterial hypertension, and other cardiovascular complications. Supporting breathing during sleep with NPPV reverses this whole process. There are many theoretical reasons to start nocturnal NPPV early in ALS.

1. Provide rest for weak diaphragm so breathing and functional status is better during the day.
2. Improve QOL
3. Improve sleep quality
4. Allow respiratory centers to regain normal function, particularly response to O₂ and CO₂.
5. Reduce risk of sudden death due to nocturnal hypoventilation and/or arrhythmia
6. Improve nocturnal and daytime (awake) gas exchange
7. Stabilize the upper airway for both ventilation and effective handling of secretions
8. Prevent atelectasis and improve lung compliance.
9. Provide time for patient and family caregivers to become experienced with equipment before an acute respiratory infection or acute respiratory failure becomes life-threatening and/or requires hospitalization.
10. Provide the hands-on opportunity to try respiratory assistance devices to better inform patients regarding decisions about the use of long-term NPPV and /or tracheostomy ventilation.
11. Improve skills for effective cough as an important part of the instruction for NPPV

3. How do I initiate NPPV in my ALS patients?

NPPV should be started at low pressures in order to improve a patient's initial tolerance to the device. Generally the inspiratory pressure (IPAP) is set at 6-8 cm H₂O and the expiratory pressure (EPAP) is set at 3-5 cm H₂O. The IPAP can then be titrated by 1-2 cm increments based on tolerability and symptoms of hypoventilation. The device should be placed on a spontaneous timed mode (ST) with a backup rate set at the patient's nocturnal respiratory rate (generally 8-10). Different interfaces including nasal mask, nasal pillows, full face masks or mouth pieces should be used to maximize patient comfort. Patients should be encouraged to alternate interfaces in order to reduce skin/nasal irritation. The mask may be used initially without the headgear by having the patient hold the mask gently against their face. The headgear can then be added when the patient is more comfortable.

Once NPPV is initiated, the respiratory therapist should evaluate the patient daily for the first week and then twice a week for the next 3 weeks to address any potential problems and review and adjust the ventilator settings and interfaces according to patient need. Patient acclimation to NPPV may be enhanced by starting with shorter periods of daytime usage (i.e. 2 hours) and gradually increasing the length of time used to the full night plus additional daytime use if necessary. A heated humidifier and a nasal steroid can both be prescribed if the patient develops symptoms of nasal dryness or congestion.

4. How do I follow my ALS patients on NPPV and when should tracheostomy ventilation be considered?

Patients should be questioned at each clinic visit regarding whether they are experiencing any symptoms suggesting nocturnal hypoventilation. If so, the IPAP pressure can be empirically increased. A more objective assessment can be obtained by performing a nocturnal oximetry study. These are routinely done every 3-6 months. If the study shows evidence of significant oxygen desaturations below 90%, the IPAP should be increased to eliminate the desaturations. The use of supplemental oxygen is not recommended except when palliative care is appropriate. Tracheostomy ventilation should be considered if: a) the patient is unable to tolerate NPPV, b) the patient is unable to manage airway secretions despite optimal medical management, c) the patient is dependent on NPPV for > 16 hours/d, d) there is evidence of worsening hypoventilation which cannot be corrected with an increase in IPAP (pCO₂ > 55mm Hg or arterial pH<7.30), e) both patient and family are committed.

5. What else can be done to maximize the benefit of NPPV and minimize the risk of respiratory infections?

Although non-invasive ventilatory support can be very effective in managing symptoms of hypoventilation, another major difficulty is management of secretions, especially during intercurrent respiratory infections. Patients with a Peak Cough Expiratory Flow (PCEF) of > 270 L/min are able to effectively cough and clear their airway. When PCEF falls below 270 L/min, patients require external support in order to clear secretions (10). This can be provided by a mechanical insufflator-exsufflator.

Mechanical insufflation-exsufflation involves the delivery of an insufflation of pressurized air (30-50 cm H₂O) followed by an immediate forced exsufflation of negative pressure (30-50 cm H₂O). The negative pressure is typically maintained for 1-3 sec. The in-exsufflator is a portable device that interfaces with the airway via a mouthpiece or naso-oral mask. The use of mechanical in-exsufflation safely allows patients with respiratory tract infections and profuse mucous production to clear their secretions and permit the ongoing use of non-invasive ventilatory support (11). Patients who are unable to achieve PCEF sufficient to clear respiratory mucous (defined as a PCEF rate of 270 L/min) should be instructed in mechanical insufflation-exsufflation (MI-E) techniques using a Cough Assist machine. They can then use this MI-E device on an as-needed basis to clear respiratory secretions. The caregiver should be taught to deliver MI-E to patients via an anesthesia mask. The insufflation and exsufflation pressures should be set to the maximum comfortable level tolerated by each patient in order to eliminate airway secretions. In general, inspiratory pressures are set at 20-40 cm H₂O and expiratory pressures are set at 5-20 cm H₂O.

Bach recently reported a retrospective review of 101 ALS patients evaluated from 1990-2000 (12). Patients were initiated on NPPV when symptomatic for hypoventilation and trained in MI-E when PCEF decreased to <270 L/min. Sixteen patients used part-time NPPV for 17.5 +/- 13.0 months, then full-time NPPV for 14.1 +/- 12.6 months before tracheostomy. Nineteen patients used part-time and full-time NPPV for 25.2 +/- 19.8 months and 17.5 +/- 13.3 months, respectively without undergoing tracheostomy. Bach concluded that NPPV along with MI-E can permit prolonged survival and delay the need for tracheostomy in a significant minority of ALS patients by > 1 year.

Another device that can be currently prescribed for assistance in airway secretion management is "The Vest". The Vest is worn like a jacket by the patient and is connected to an air generator that rapidly inflates and deflates the vest gently resulting in up to 25 chest wall compressions/second. Mucous is dislodged from the bronchial walls by this process and moves to the central airways where it can either be removed by coughing, by use of a MI-E, or by suctioning. In a comparative study of 29 patients with cystic fibrosis, The Vest System cleared three times more mucous than chest percussive therapy. Over 160 ALS patients to date have used The Vest system and a pilot study is currently being planned. Patients will use The Vest for six weeks and then abstain for six weeks for at least two cycles. Patients will use The Vest for two daily sessions of up to 20 minutes each.

In addition to using these techniques for cough augmentation, it is important to administer a pneumococcal (every 10 years) and an influenza vaccine (annually). Oral secretions should be controlled with anti-cholinergics and adequate hydration should be ensured with early PEG tube placement.

References:

1. Aboussousan LS, Khan SU, Meeker DP, Stelmach K, Mitsumoto H. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. *Ann Intern Med* 1997;127:450-453.
2. Kleopa K, Sherman M, Neal B, Romano G, Heiman-Patterson T. BiPAP improves survival and rate of pulmonary function decline in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* 1999;164(1):82-88.
3. Aboussousan LS, Khan SU, Banerjee M, Arroliga AC, Mitsumoto H. Objective measures of the efficacy of noninvasive positive –prssure ventilation in amyotrophic lateral sclerosis. *Muscle Nerve* 2001;24:403-409.
4. Lyall RA, Donaldson N, Fleming T, Wood C, Newsom-Davis I, Polkey MI, Leigh PN, Moxham J. A prospective study of quality of life in ALS patients treated with noninvasive ventilation. *Neurology* 2001;57:153-156.
5. Miller RG, Rosenburg JA, Gelinas DF, Mitsumoto H et al and the ALS Practice Parameters Task Force. Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review). *Neurology* 1999;52:1311-1323.
6. Krivickas LS. In Mitsumoto H (ed). *Amyotrophic Lateral Sclerosis*, F.A. Davis 1998, pp. 388-389.
7. The Respiratory Assist Devices – New Policy, A new Durable Medical Equipment Regional Carrier (DMERC) Regional Medical Review Policy (RMRP) on Respiratory Assist Devices
<http://www.cignamedicare.com/docs/dmerc/06dradarticle.htm> (DMERC) processing claims for durable medical equipment, prosthetics, orthotics & supplies.
<http://www.adminastar.com/anthem/affiliates/adminaster/dmerc/index.html>
8. Jackson CE, Rosenfeld J, Moore D, Bryan WW, Barohn RJ, Wrench M, Myers D, Herberlin L, King R, Smith J, Gelinas D, Miller RG. A preliminary evaluation of a porspective study of pulmonary function studies and symptoms of hypventilation in ALS/MND patients. *Journal of the Neurological Sciences* 2001; 191:75-78.
9. Gay PC, Westbrook PR, Daube JR, Litchy WJ, Windebank AJ, Iverson R. Effects of alterations in pulmonary function and sleep variables on survival in patients with amyotrophic lateral sclerosis. *Mayo Clin Proc* 1991;66:686-694.
10. Bach, J. *Guide to the Evaluation and Management of Neuromuscular Disease*. Hanley & Belfus Inc. 1999; pp. 107-109.
11. Bach, JR. Mechanical insufflation-exsufflation: comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. *Chest* 104:1553-1562.
12. Bach J. Amyotrophic lateral sclerosis: prolongation of live by non-invasive respiratory aids. *Chest* 2002;122:92-98.