Effect of Noninvasive Positive-Pressure Ventilation on Survival in Amyotrophic Lateral Sclerosis

Louafi Sami Aboussouan, MD; Saeed U. Khan, MD; David P. Meeker, MD; Kay Stelmach, RRT; and Hiroshi Mitsumoto, MD

Background: Noninvasive positive-pressure ventilation may benefit patients with amyotrophic lateral sclerosis and respiratory insufficiency.

Objective: To determine 1) whether patients tolerant of noninvasive positive-pressure ventilation have better survival than intolerant patients and 2) whether bulbar symptoms account for intolerance of noninvasive positive-pressure ventilation.

Design: Observational cohort study.

Setting: Tertiary care referral center.

Patients: 39 patients with amyotrophic lateral sclerosis who were treated with noninvasive positive-pressure ventilation.

Intervention: Noninvasive positive-pressure ventilation was started for patients with new orthopnea, new hypercapnia, or both. Patients were divided into two groups: those tolerant of and those intolerant of noninvasive positive-pressure ventilation.

Results: The risk for death from onset of respiratory insufficiency was higher for intolerant patients than for tolerant patients (relative risk, 3.1 [95% CI, 1.8 to 9.6]). Moderate or severe bulbar symptoms were more prevalent among intolerant patients than among tolerant patients (67% compared with 33%; P = 0.04).

Conclusions: Among patients with amyotrophic lateral sclerosis, those who are tolerant of noninvasive positive-pressure ventilation have better survival than do those who are intolerant. Bulbar symptoms partially account for intolerance of noninvasive positive-pressure ventilation.

Respiratory failure is the most common cause of death in patients with amyotrophic lateral sclerosis (1). Nocturnal noninvasive positive-pressure ventilation is the treatment of choice for patients with chronic respiratory insufficiency secondary to slowly progressive neuromuscular diseases (2). However, the optimal use of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis remains undefined, and use of this intervention has raised several concerns.

For instance, the course of amyotrophic lateral sclerosis varies, and some patients have a rapid decline in lung function (3). In addition, approximately 50% of patients with neuromuscular diseases or sleep apnea are intolerant of positive-pressure devices (4, 5). Some investigators have discouraged use of this ventilation in patients with amyotrophic lateral sclerosis and bulbar symptoms (2, 6, 7). Further concern was raised by the finding of a survival disadvantage, relative to controls, in patients with Duchenne neuromuscular dystrophy who began receiving noninvasive positive-pressure ventilation (8).

Ethical considerations may preclude placebo-controlled trials in patients with amyotrophic lateral sclerosis because of the putative benefits of noninvasive positive-pressure ventilation (2) and the rapidly fatal nature of the disease (9). We therefore sought to determine 1) whether patients with amyotrophic lateral sclerosis and respiratory insufficiency who are tolerant of noninvasive positive-pressure ventilation have a survival advantage compared with those who are intolerant and 2) whether bulbar symptoms account for intolerance of noninvasive positive-pressure ventilation.

Methods

Study Sample

Our study was done at the Cleveland Clinic Foundation between March 1993 and February 1996. The diagnosis of amyotrophic lateral sclerosis was based on the El Escorial World Federation of Neurology criteria (10). Follow-up evaluation at the neuromuscular clinic, including spirometry, was done every 3 to 6 months and as necessary. All patients who had dyspnea on exertion, hypercapnia, or an FVC less than 60% of the predicted value were referred to the pulmonary clinic, where a clinical evaluation, pulmonary function tests, and tests for daytime arterial blood gases were done every 1 to 2 months. Bulbar symptoms were assessed by using the speech and swallow components of the amyotrophic lateral sclerosis severity scale and were graded as “absent to mild” or “mod-
erate to severe” on the basis of the most advanced instance of speech or swallowing impairment (11).

**Pulmonary Function Tests**

The neuromuscular clinic used a Puritan-Bennett PB 100 spirometer (Puritan-Bennett, Wilmington, Massachusetts). The pulmonary clinic used a Cybermedics spirometer (Collins/Cybermedics, Braintree, Massachusetts) and an inspiratory force meter (Boehringer, Norristown, Pennsylvania) to measure maximal inspiratory and expiratory pressures. The predicted values of Crapo and colleagues (12) were used for FVC and FEV\(_1\), and the predicted values of Black and Hyatt (13) were used for maximal respiratory pressures.

**Respiratory Assistance Devices**

Noninvasive positive-pressure ventilation was offered as an alternative to tracheostomy to patients with new orthopnea, hypercapnia, or both (PCO\(_2\) ≥ 45 mm Hg). The devices used were a volume-controlled ventilator (PLV-100, Life Care Products, Lafayette, Colorado) in assist-control mode or a bilevel positive-pressure device (BiPAP, Respironics, Inc., Murrysville, Pennsylvania) in spontaneous-timed mode (the latter was added as an option after September 1994). Patients were ventilated in the supine position while in clinic. Tidal volume (for the volume-controlled ventilator) or pressure (for the bilevel positive-pressure device) were initially adjusted for chest rise, leaks, and patient comfort and were adjusted on subsequent visits to control hypercapnia and dyspnea. The ultimate choice of a device was made by the patient after the two devices had been sampled. Patients were instructed to use noninvasive positive-pressure ventilation nightly as tolerated and as necessary in the daytime. On subsequent visits, alternate interfaces were used for mask-related problems, nasal steroid sprays were used for nasal congestion, and suction machines or mechanical insufflation-exsufflation were used for clearance of secretions (14). Tolerance was defined as the ability to sleep nightly while receiving noninvasive positive-pressure ventilation for at least 4 consecutive hours.

**Statistical Analysis**

Baseline values in the tolerant and the intolerant groups were compared by using an unpaired t-test for normally distributed data and by using the Mann-Whitney U test for continuous data that were not normally distributed. The Pearson chi-square test was used to compare proportions between the groups. Kaplan-Meier estimates of the survival curves (15) were determined for pertinent subgroups. The log-rank test was used to compare survival curves, and the Cox proportional hazards model was used to simultaneously adjust for multiple potential confounders (bulbar symptoms, type of device, maximal expiratory pressure, and use of study drugs) (15). A significance level of 0.05 was used.

**Results**

Sixty-six patients with amyotrophic lateral sclerosis were seen in the pulmonary clinic between March 1993 and February 1996. Fifteen developed neither orthopnea nor hypercapnia. In 4 patients,
patients, tolerance of noninvasive positive-pressure ventilation could not be determined before death. One patient was lost to follow-up. The remaining 39 patients were included in this observational cohort. Thirteen were receiving neuroprotective agents that can modify the course of amyotrophic lateral sclerosis: brain-derived neurotrophic factor (6 patients), gabapentin (4 patients), riluzole (2 patients), and ciliary neurotrophic factor (1 patient).

Comparison of Intolerant and Tolerant Patients

Relevant characteristics at the onset of respiratory insufficiency were well matched between our two study groups (Table). Eighteen of the 39 patients (46%) who began receiving noninvasive positive-pressure ventilation tolerated the intervention. Although moderate or severe bulbar symptoms were twice as prevalent in intolerant patients as in tolerant patients, 30% of patients with moderate or severe bulbar symptoms were tolerant of noninvasive positive-pressure ventilation. More tolerant patients than intolerant patients were using the bilevel positive-pressure device.

Survival from Onset of Respiratory Insufficiency

Twenty-nine patients died; 9 were tolerant of noninvasive positive-pressure ventilation and 20 were intolerant. All had refused invasive ventilation. The relative risk for death was 3.1-fold greater in intolerant patients than in tolerant patients (Figure, top). After stratification for the absence (Figure, middle) or presence (Figure, bottom) of moderate or severe bulbar symptoms, a significant survival benefit persisted within each stratum for tolerant patients.

A Cox proportional hazards model that adjusted for potential confounders (bulbar symptoms, type of device, use of neuroprotective agents, and maximal expiratory pressure) indicated that a significant survival benefit persisted for tolerant patients (relative risk for intolerant compared with tolerant patients, 1.72 [95% CI, 1.03 to 3.03]; \( P = 0.04 \)). None of the other covariates had a significant effect on survival.

Discussion

Our findings indicate that among patients who start receiving noninvasive positive-pressure ventilation at the onset of respiratory insufficiency caused by amyotrophic lateral sclerosis, those who tolerate this intervention have a significant survival advantage compared with those who cannot tolerate it. This result cannot be attributed to differences in pulmonary function, respiratory muscle strength, age at onset, time from onset of disease to initiation of noninvasive positive-pressure ventilation, bulbar
symptoms, use of neuroprotective agents, or rate of decline of lung function before initiation of therapy.

Bulbar symptoms partially account for intolerance of noninvasive positive-pressure ventilation, but they are unlikely to affect survival (1, 9, 16). For instance, our data show that the improved survival in patients who are tolerant of noninvasive positive-pressure ventilation is maintained after controlling for bulbar symptoms. Therefore, 30% of our patients with moderate or severe bulbar symptoms were tolerant of mask ventilation and benefited from noninvasive positive-pressure ventilation. Complications from noninvasive positive-pressure ventilation contributed to intolerance but were limited to discomfort caused by mask fit or air pressure, pressure over the bridge of the nose, air leaks, and nasal congestion.

Although not designed to address different modes of ventilation, our study suggests that tolerance is better with pressure-limited ventilation than with volume-limited ventilation. Nonetheless, tolerance of either intervention was associated with a survival benefit.

Ethical considerations precluded use of a control group. In addition, few historical data are available on survival from the time of onset of respiratory insufficiency in patients with amyotrophic lateral sclerosis. However, in a study by Fallat and coworkers (3), 14 of 16 patients with amyotrophic lateral sclerosis (88%) who had an FVC of 50% or less of the predicted value died within 5 months; all 16 died within 9 months. This course is consistent with that of our patients who were intolerant of noninvasive positive-pressure ventilation.

Our results are at odds with those of Raphael and colleagues (8), who found a survival disadvantage in patients treated with noninvasive positive-pressure ventilation for muscular dystrophy. Differences in study methods (such as exclusion of patients with hypercapnia) and patient population probably account for this discrepancy.

Limitations of our study include lack of a control group, use of different ventilation devices, use of neuroprotective agents that may have affected the course of amyotrophic lateral sclerosis, and a relatively small number of patients. In addition, we did not objectively address quality-of-life issues (although most tolerant patients reported satisfaction with the intervention, which was particularly reflected in improved sleep). Further, we did not identify the optimal timing for initiation of noninvasive positive-pressure ventilation. Our intervention could be considered to have been given late but often warrants reimbursement by insurance carriers.

In summary, patients with amyotrophic lateral sclerosis who are tolerant of noninvasive positive-pressure ventilation at the onset of respiratory insufficiency have better survival than do patients who are intolerant. Bulbar symptoms only partially account for intolerance of noninvasive positive-pressure ventilation but should not interdict a trial of noninvasive positive-pressure ventilation. Our study expands recommendations for the use of noninvasive positive-pressure ventilation to some patients with bulbar symptoms and more rapidly progressive neuromuscular diseases, such as amyotrophic lateral sclerosis.

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References

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