SHORT REPORT

ABSTRACT: Noninvasive ventilation (NIV) appears to improve survival and quality of life in patients with amyotrophic lateral sclerosis (ALS), but little is known about predictors of NIV tolerance. NIV use was assessed and clinical predictors of tolerance were investigated, using predictive modeling, in ALS patients diagnosed and followed in our clinic until death over a 4-year time period. Patients were prescribed NIV based on current practice parameters when respiratory symptoms were present or forced vital capacity was less than 50%. We prescribed NIV in 52% (72) of patients. For those prescribed NIV, information regarding tolerance was available for 50 patients, with 72% (36) tolerant to its use. Tolerance was six times more likely in limb-onset than bulbar-onset ALS patients, with a trend toward reduced tolerance in those with lower forced vital capacity at NIV initiation. Age, gender, and duration of disease were not predictors of NIV tolerance. We conclude that a majority of ALS patients who are prescribed NIV can successfully become tolerant to its use.

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PREDICTORS OF NONINVASIVE VENTILATION TOLERANCE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is clinically heterogeneous in presentation and progression of symptoms, with respiratory failure as the most common cause of death.[11] Location of symptom onset (bulbar rather than limb) and rapid rate of respiratory decline are associated with shorter survival.[10,14] Survival appears to be extended, and quality of life improved, through the use of noninvasive ventilation (NIV) for at least 4 hours per night.[2,4,12] Given the significant benefits NIV provides, its use has become the standard of care,[17] but only half of ALS patients are able to tolerate NIV to achieve these benefits.[1,12] Additionally, some studies have shown that ALS patients with more bulbar symptoms are less likely to tolerate NIV,[1,4] whereas others report no difference in tolerability between bulbar-onset and limb-onset ALS.[12] The purpose of the present study was to determine whether initial clinical features and pulmonary function tests are useful in predicting NIV tolerance among ALS patients, using a multivariable approach. Our study provides further information on factors associated with tolerance while adjusting for important confounders. These data will be helpful in clinical practice to identify those patients with the highest likelihood of being intolerant, and may also help to identify subgroups of patients in whom tolerability issues deserve further study.

Abbreviations: ALS, amyotrophic lateral sclerosis; BiPAP, bilevel positive airway pressure; BMI, body mass index; CI, confidence interval; FVC, forced vital capacity; NIV, noninvasive ventilation; OR, odds ratio; PFT, pulmonary function tests

Key words: amyotrophic lateral sclerosis; noninvasive ventilation; predictive modeling; pulmonary function tests; tolerance

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METHODS

Patients. We included patients diagnosed with definite or probable ALS[6] who were followed in our institutional ALS clinic until death between 2000 and 2003. Patients were seen every 3 months and prescribed bilevel positive airway pressure (BiPAP) when respiratory symptoms were present and either forced vital capacity (FVC) was $<50\%$[17] or mean inspiratory pressure (MIP) was <60 cm H_2O.[3] We did not start NIV until sialorrhea was effectively controlled. For sialorrhea, we used glycopyrrolate or transdermal hyoscine or, if pseudobulbar symptoms were present, amitriptyline. If patients failed or had a contraindication to pharmacologic treatment, they received botulinum toxin injections into the salivary

Table 1. Demographics and baseline clinical characteristics.

	Overall		Tolerant (n = 36), mean (SD)	Nontolerant (n = 14), mean (SD)	Tolerant vs. nontolerant (P-value)
	N	Mean (SD)			
Age	139	62.6 (12.1)	63.2 (12.3)	62.8 (11.4)	0.97
Female (%)	139	48	50	36	0.36
BMI	92	25.8 (7.1)	27.1 (7.8)	25 (4.3)	0.88
Limb onset (%)	139	63	67	29	0.01
FVC at NIV start	63	46.7 (11.8)	49.6 (10.9)	42 (12.0)	0.04
PFTs met for NIV (%)	139	83	97	93	0.48
Symptom onset to PFT criteria met (days)	115	738 (689.4)	800 (793.3)	694.9 (577.9)	0.51
Diagnosis to NIV (days)	72	341 (435.6)	293.8 (349.8)	378.4 (370.2)	0.71
Diagnosis to death (days)	139	671 (632.2)	701 (449.5)	946.1 (822.4)	0.63

BMI, body mass index; FVC, forced vital capacity (percent predicted); PFT, pulmonary function test; NIV, noninvasive ventilation.

glands.[8] Pressures were begun at 8 cm H_2O inspiratory positive airway pressure (IPAP) and 3 cm H_2O expiratory positive airway pressure (EPAP),[15,16] using heated humidification and NasalAire interfaces to minimize nasal congestion and claustrophobia from large masks, respectively.[15] If nasal congestion continued, intranasal steroid sprays were prescribed. Patients were contacted after 1 week by telephone to determine whether respiratory symptoms had improved. If patients continued to have respiratory symptoms, the inspiratory positive airway pressure was increased by 2 cm H_2O increments weekly until symptoms improved.[15] The study was approved by the local institutional review board with a waiver of informed consent.

Clinical Classification. A retrospective chart review was conducted in order to collect information on the dates of ALS symptom onset, diagnosis, NIV initiation, and death, in addition to age at symptom onset, gender, smoking status at diagnosis, site of symptom onset, FVC at diagnosis, and FVC at the time of NIV initiation. Patients were classified as tolerant to NIV if they used it nightly for ≥4 hours as documented at each clinic visit.

Statistical Methods. Proportions and means with standard deviations were calculated for demographic variables and baseline patient characteristics. A chi-square test was performed to assess the relationship between gender or site of symptom onset and prescription of NIV. The relationship between tolerance and baseline variables was assessed using a chi-square test for dichotomous variables and Wilcoxon's rank sum test for continuous variables. No adjustment for multiple comparisons was made. The relationship between FVC (dichotomized: low ≤80%, high >80%) and location was also assessed using a chi-square test. Univariable logistic regression was used to assess the relationship between NIV tolerance and the following variables: age; time from symptom onset to NIV initiation; symptom onset location (bulbar vs. limb); gender; and FVC at the time of NIV initiation. A multivariable logistic regression model was then fit with these five explanatory variables. Predictors were selected in a prespecified fashion based on their biologically plausible relationship with the outcome. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable in the models. Internal model validation was performed with bootstrapping (200 times with replacement).[9] The overall model performance was assessed by calculating the C value. S-Plus 6.1 software (Insightful Corp., Seattle, Washington, 2002) was used for the analyses.

RESULTS

Clinical Findings. There were 139 patients with ALS who fulfilled selection criteria. Baseline characteristics are shown in Table 1. Overall, 72 (52%) were prescribed NIV. There were no differences in prescription of NIV by gender (P = 0.44) or site of symptom onset (P = 0.58). Of those patients who were prescribed NIV, information on tolerance was available for 50 (70%). Of those 22 for whom tolerance could not be determined, the reason was as follows: 18 did not survive long enough for a determination to be made; 2 were lost to follow-up; and 2 had inadequate chart documentation. Thirty-six (72%) were tolerant to NIV, and 14 (28%) were not. Comparison of baseline variables for tolerant and nontolerant patients is shown in Table 1. Patients who were tolerant were more likely to have limb-onset symptoms and have higher FVCs at NIV initiation.

Table 2. Results of multivariable predictive model for NIV tolerance.

	OR	95% CI
Age	1.82	0.50, 6.58
FVC at NIV start	2.48	0.65, 9.45
Limb onset	6.25	1.09,33.33
Time from symptom to NIV start	1.15	0.50, 2.65
Female	4.32	0.74,25.19

Referent group for limb onset is bulbar onset. Referent group for female is male. OR, odds ratio; CI, confidence interval; FVC, forced vital capacity (percent predicted); NIV, noninvasive ventilation.

There were 119 patients with a documented FVC within 3 months of diagnosis. Of these patients, 84 (71%) had FVC $\leq$ 80%. Of those with FVC $>$ 80%, 8 (23%) had bulbar-onset and 27 (77%) had limb-onset symptoms. Of those with FVC $\leq$ 80%, 33 (39%) had bulbar-onset and 51 (61%) had limb-onset symptoms. There was no difference in the proportion of bulbar-onset and limb-onset in those with high or low FVCs ($P = 0.09$).

Predictors of NIV Tolerance. In the univariable analyses, limb-onset disease was associated with NIV tolerance [OR = 5 (95% CI: 1.30, 20.0)]. FVC at NIV start time was not significantly associated with NIV tolerance [OR = 2.9 (95% CI: 0.96, 8.64)], despite an evident trend. Age [OR = 1.36 (0.43, 4.33)], female gender [OR = 1.80 (0.50, 6.43)], and time from symptom onset to NIV initiation [OR = 1.24 (0.65, 2.38)] were not associated with NIV tolerance in the univariable models.

In the multivariable model, only limb onset was independently associated with NIV tolerance [OR = 6.25 (1.09, 33.33)]. No other predictive variable was associated with NIV tolerance in the multivariable model (Table 2). The C value of the overall multivariable model was 0.83. Although the bootstrapped model did degrade somewhat in performance, the C value of 0.73 suggested moderate model performance.

DISCUSSION

NIV was prescribed to over half of ALS patients in our clinic. Other investigations of NIV use have demonstrated similar results, with 70 of 122 (57%)[12] patients with FVC $<$ 50% being prescribed NIV. A more recently published review of 92 U.S. and Canadian sites reported an NIV use prevalence of 33% among ALS patients with FVC $\leq$ 50%.[13] The same study demonstrated that patients with lower incomes and women were less likely to be prescribed NIV, suggesting that these patients receive less aggressive therapy.[13] We did not find that women were less likely to be tolerant to NIV, demonstrating that female gender does not negatively impact the successful use of NIV.

NIV tolerance, assessed as nocturnal use $>$4 hours per night, was achieved in 70% of our ALS patients. This is much higher than the previously reported NIV tolerance of 54%[12] and 49%[1] for ALS patients. As these referenced comparison studies were performed prior to publication of the practice parameters suggesting survival benefit related to NIV use,[17] our patients could have been more motivated to use NIV than the patients reported previously, as they may have been more aware of the potential benefits. Practitioners may also have been more motivated to encourage compliance and to resolve NIV problems. A recent review of patients enrolled in the ALS CARE database from over 90 different sites in North America compared disease management before and after practice parameters were published, and demonstrated a significant increase in NIV use from 9% to 21% of database patients following publication.[5] However, 79% of patients in the ALS CARE database with FVC $<$ 40%, thus meeting the recommended prescribing criteria of both the American Academy of Neurology[17] and American College of Chest Physicians,[3] were not using this treatment. Approximately half of this 79% were never offered NIV and the other half either refused or could not tolerate NIV treatment.[5] In our clinic, education about NIV is provided in person to the patients, supplemented by phone contact as detailed earlier. We employ the techniques described in the Methods section to promote tolerance. Perhaps these measures improved NIV tolerability, although we suspect our management of NIV intolerance is similar to that of other specialized ALS clinics. Nonetheless, the high tolerance of NIV use reported here underscores the opportunity for usefulness[2,4,12] of NIV in ALS patients and should be considered when prescribing NIV.

We found that patients with limb-onset symptoms were six times more likely to tolerate NIV than those with bulbar-onset ALS. Our findings are in agreement with two previous prospective studies.[1,4] Both studies also supported the association between bulbar symptoms and NIV intolerance, although these analyses did not adjust for other clinical characteristics. Our results do, however, contradict a previous retrospective analysis.[12] Bulbar-onset ALS patients are already known to have a poorer prognosis than limb-onset patients at diagnosis[10,14] and are further disadvantaged by higher intolerance to NIV. Further study into the reasons for NIV intolerance in patients with prominent or early bulbar symptoms may disclose ways to improve tolerance in this ALS subpopulation.

Pulmonary function tests are used as a guide to begin NIV in ALS patients and are assessed at routine intervals per practice guidelines.[17] Although not statistically significant, we found a trend toward intolerance in patients with a lower FVC at the time of NIV initiation in the multivariable model, consistent with previous work.[1,4] Although caution is required in interpreting this finding, this trend is supportive of the hypothesis that earlier administration of NIV, prior to meeting standard-of-care criteria based on respiratory muscle weakness, may increase NIV tolerance. This is supported by Bourke et al., who described good NIV tolerance in ALS patients with symptoms of orthopnea despite average FVC $> 50\%$.[4] Examination of the relationship between tolerance and FVC at the time of NIV initiation in a larger data set may clarify this important clinical issue.

FVC was $\leq 80\%$ predicted within 3 months of diagnosis in $>70\%$ of all ALS patients in this study. In a cohort of 218 patients with motor neuron disease, Fallat et al. demonstrated that 106 patients (49%) had FVC $< 80\%$ at initial evaluation.[7] In contrast, we found that there was no difference between the percentage of bulbar-onset and limb-onset ALS patients with FVC $\leq 80\%$ within 3 months of diagnosis. Although bulbar-onset patients have a poorer prognosis and appear to be less tolerant to NIV, they did not have a lower FVC at initial presentation compared with limb-onset ALS patients.

The explanatory power of the statistical models was limited by the small numbers in the data set. Although the use of five clinical predictors in the multivariable model may have resulted in overmodeling, we attempted to compensate for this by internally validating the model with bootstrapping. Bootstrapping is a statistical technique that uses iterative sampling with replacement to calculate a conservative estimate of model performance, estimating the model's discriminatory ability if applied to an outside data set.[9] The results should nonetheless be validated in an external data set. The use of subjective reporting of NIV tolerance, rather than objective interrogation of NIV machines, and the retrospective nature of this study also represent limitations.

In conclusion, our findings indicate that a majority of ALS patients administered NIV (70% in this study) are tolerant of it. Assessment of predictors of NIV tolerance only identified limb onset of ALS symptoms as an independent predictor, although higher FVC at NIV initiation may also be predictive of NIV tolerance. Importantly, duration of disease and age were not predictors of tolerability and should not be considered reasons to withhold NIV.

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