ABSTRACT: The impact of noninvasive positive-pressure ventilation (NIPPV) on pulmonary function studies, quality of life, and survival was assessed in patients with amyotrophic lateral sclerosis. NIPPV did not change the rate of decline of the forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) (2.31 and 2.09 percent-predicted points per month, respectively). NIPPV resulted in a drop of FEV_1 by 5.94 percent-predicted points ($P = 0.07$), and of maximal inspiratory pressure by 6.33 percent-predicted points ($P = 0.11$). The change in FEV_1 and FVC pre- and postintervention correlated with the corresponding change in maximal inspiratory pressure. Fatigue and mastery scores were improved by NIPPV. Median survivals in patients intolerant and tolerant of NIPPV were 5 and 20 months, respectively ($P = 0.002$). Although NIPPV has no impact on the rate of decline of lung function and may have deleterious effects on spirometric measures, it may improve quality of life and survival.

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OBJECTIVE MEASURES OF THE EFFICACY OF NONINVASIVE POSITIVE-PRESSURE VENTILATION IN AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis is a progressive neuromuscular disorder, which almost uniformly leads to death from respiratory failure.[5] Noninvasive positive-pressure ventilation (NIPPV) has been used as an alternative or as a bridge to tracheostomy, and has been considered the treatment of choice for patients with respiratory insufficiency due to neuromuscular diseases.[11] Although many studies suggest that NIPPV increases survival,[1,6,16,20,24] recent publications emphasize the need to better identify objective measures of the efficacy of this intervention.[14,19]

Similarly, the optimal timing for initiation of NIPPV has been a focus of interest.[19] Current rec-

ommendations are to initiate NIPPV when the FVC drops to 50% of predicted value.[19] It is unclear whether NIPPV alters the natural course of amyotrophic lateral sclerosis, and therefore whether earlier initiation would result in greater survival benefit. For instance, there is some evidence to suggest that the rate of decline of lung function may be slowed after initiation of NIPPV in patients with Duchenne muscular dystrophy,[22,25] and amyotrophic lateral sclerosis.[16]

To objectively address some measures of efficacy of NIPPV, we sought to determine whether this intervention improves spirometric measures of lung volumes, daytime arterial blood gases, indices of respiratory muscle strength, survival, and quality of life. We also assessed whether NIPPV slows the decline in lung function, thereby providing justification for earlier initiation of intervention.

MATERIALS AND METHODS

Study Sample. The study included all patients with a diagnosis of probable or definite amyotrophic lat-

eral sclerosis based on the El Escorial World Federation of Neurology criteria,[4] who were started on NIPPV at the Cleveland Clinic Foundation over a period of 5 years from March 1993 to February 1998. The neuromuscular clinic evaluation included screening spirometry every 3–6 months. Detailed pulmonary evaluation was initiated and repeated every 1–2 months once patients developed dyspnea on exertion, orthopnea, or a forced vital capacity (FVC) below 60% of predicted value on screening spirometry. This evaluation included clinical assessment, spirometry, measurement of maximal inspiratory and expiratory pressures, and determination of arterial blood gases on room air. Bulbar symptoms were classified as "absent to mild" or "moderate to severe" based on the most severe instance of speech or swallowing impairment as assessed from the corresponding components of the amyotrophic lateral sclerosis severity scale.[13]

Assessment of Quality of Life. We used the Chronic Respiratory Index Questionnaire to assess quality of life in a subset of our patients.[10] This index evaluates quality of life along four dimensions: dyspnea, fatigue, emotional, and sense of control over the disease (mastery), and was administered pre- and postinitiation of NIPPV. An increase in score indicates improvement and minimal clinically important score differences are 3.0, 2.0, 4.0, and 2.0 for dyspnea, fatigue, emotional, and mastery, respectively.[10]

Pulmonary Function Tests. Spirometry was performed with a Puritan-Bennett PB-100 spirometer (Puritan-Bennett, Wilmington, MA) in the neuromuscular clinic, and a Cybermedics spirometer (Collins/Cybermedics, Braintree, MA) in the pulmonary clinic. The American Thoracic Society spirometry reproducibility criteria were applied.[2] Measurements of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were performed on an inspiratory force meter (Boehringer, Norristown, PA). Predicted values of Crapo et al. were used for spirometric values,[7] and Black and Hyatt[3] for maximal respiratory pressures.

Respiratory Assistance Devices. Noninvasive positive-pressure ventilation was proposed to all patients with new symptoms of orthopnea and/or hypercapnia (PCO_2 equal to or greater than 45 mmHg). Patients who proceeded to a tracheostomy after failure or intolerance of noninvasive ventilation were excluded.

The devices consisted of either a volume-controlled ventilator (PLV-100) in assist-control mode, or a bilevel positive-pressure device (BiPAP) in spontaneous-timed mode (both from Respironics, Inc., Pittsburgh, PA), with tidal volume (PLV-100) or pressures (BiPAP) adjusted in clinic to chest rise, leaks, and patient comfort. Patients were instructed to use NIPPV for as long as tolerated after retiring to bed and as necessary in the daytime. Tolerance was strictly defined as the ability to sleep with the device for at least 4 consecutive hours nightly. For instance, an intolerant patient could be one who used NIPPV for more than 4 h/day but was unable to sleep with the device on, or whose sleep was interrupted, thereby preventing use of the device for 4 consecutive hours while asleep. To maximize compliance, alternate interfaces were used as necessary, nasal steroid sprays were used for nasal congestion, and suction devices for clearance of secretions.

Statistical Methods. Longitudinal or repeated-measures analysis was used for the investigation of individual changes of PO_2, PCO_2, percent of predicted value for FVC, FEV_1, and maximal inspiratory and expiratory pressures, and for assessing the effect of NIPPV intervention on the rates of change. Time intervals between measurements were expressed in days. Mixed effects modeling for repeated measures was employed to test the hypothesis that NIPPV improves spirometric measures, daytime arterial blood gases, and respiratory muscle strength, and slows the decline in lung function. Patients in our study had different numbers of repeated measures on the outcomes, as well as varying time intervals between measurements. Mixed effects models provide a useful alternative to classic multivariate regression techniques for modeling such data.

Our models included random patient-specific intercept and slope to account for the natural heterogeneity in the population. This heterogeneity would be expected due to uncontrolled factors affecting when the diagnosis was made and affecting the natural course of amyotrophic lateral sclerosis in our patient population. The fixed-effects part of our model included tolerance of NIPPV, linear and quadratic effects of time expressed in days, effect of NIPPV intervention, and time × intervention interactions. For the covariance model, we fitted several structures, and the model for final inference was selected based on Akaike's information criterion (AIC) and Schwarz's bayesian criterion (BIC).[26] Based on both criteria, a spatial power law structure gave the best fit for the covariance model, and inferences reported for the fixed effects are based on this model. These analyses were performed using PROCMIXED in SAS (SAS Institute, Cary, NC).

Pearson correlation coefficients were calculated to assess possible linear relationships between the change in spirometric indices and change in respiratory muscle strength indices immediately pre- and postintervention. Multiple linear regression analysis was performed to adjust for the varying time lag between the intervention and first postintervention measurements. The Wilcoxon signed-rank test was used for comparison of paired variables that were not normally distributed (e.g., comparison of variables pre- and postintervention). A two-sample t-test was used to compare mean FVC, MIP, MEP, and NIPPV use between tolerant and intolerant patients, and Fisher's exact test was used for comparison of proportions. Median survivals between tolerant and intolerant groups were derived from Kaplan–Meier lifetables, and a log-rank test was used to compare survival curves. The Cox proportional hazards model was used to simultaneously adjust for potential confounders of survival. All analyses were performed using SAS, version 6.12 (SAS Institute).

RESULTS

Sixty patients with amyotrophic lateral sclerosis were started on noninvasive ventilation. Ten patients had a single visit and/or had insufficient data collected before death, and 3 patients underwent tracheostomy after intolerance or failure of NIPPV. The remaining 47 patients (15 women and 32 men) were chosen for study. The average age was 62 years (range 32–79 years). Mean FVC and FEV_1 at initiation of NIPPV were 41% (range 16–70%) and 44% (range 17–78%) of predicted values, respectively. The FVC and FEV_1 measurements were reproducible in 62% and 68% of spirometries, respectively. A significantly larger number of spirometries was obtained pre- compared to post-NIPPV (140 pre- vs. 89 post-NIPPV, representing an average of 3.0 per patient vs. 1.9 per patient, respectively, $P = 0.02$). The mean time interval between measurements was significantly shorter after initiation of NIPPV (127 days pre- vs. 74 days post-NIPPV, $P = 0.02$).

Twenty-three patients (48.9%) were tolerant of NIPPV and 24 (51.1%) were intolerant. Features at the onset of the disease, rate of decline of lung function, and impact of NIPPV for the two groups are shown in Table 1. The findings closely parallel those from our earlier survival study involving a subset of this patient population.[1] Overall, the prevalence of moderate-to-severe bulbar symptoms was higher in patients who were intolerant of NIPPV, and indices of respiratory muscle strength were lower in intolerant patients. Mean NIPPV use was 8.7 h/day (range 4–20 h) in tolerant patients and 2.6 h/day (range 0–6 h) in intolerant patients. The median survival was 5 months in intolerant patients and 20 months in tolerant patients ($P = 0.002$, Table 1). After adjusting for FVC%, MIP%, and MEP% before initiation of NIPPV, and for the presence of bulbar symptoms as potential confounders of survival, the relative risk of death in intolerant patient was sixfold that of tolerant patients ($P = 0.001$). None of the other covariates had a significant effect on survival. An analysis incorporating tolerance in the mixed-effect model revealed no significant difference between tolerant and intolerant groups with regard to the decline of lung function and the effects of NIPPV (Table 1). Accordingly, the estimates of the characteristics of interest presented in Table 2 are based on the entire set of patients.

There was a significant linear decline of FVC and FEV_1 over time (Fig. 1 and Table 2). There was also a significant quadratic change with time for both FVC and FEV_1 resulting in a progressive slowing of

Table 1. Characteristics at onset of respiratory insufficiency and effect of noninvasive ventilation stratified by tolerance versus intolerance of noninvasive positive-pressure ventilation.

Feature	Tolerant	Intolerant	P-value
Mean age ± SD (years)	59.6 ± 12.0	64.0 ± 12.8	0.23*
Men/women	18/5	14/10	0.12†
Mean FVC at start of NIPPV ± SD (% predicted value)	44.7 ± 12.4	37.4 ± 12.6	0.07*
Maximal inspiratory pressure ± SD (% predicted value)	40.9 ± 24.0	30.3 ± 13.1	0.13*
Maximal expiratory pressure ± SD (% predicted value)	32.9 ± 17.0	19.5 ± 11.0	0.01*
Presence of moderate or severe bulbar symptoms (%)	30	63	0.03†
Median survival (months)	20	5	0.002‡
Mean NIPPV use ± SD (range) (hours)§	8.7 ± 3.9 (4–20)	2.6 ± 2.1 (0–6)	<0.0001*
Rate of change of FEV_1 ± SEM (% predicted value/month)	−1.94 ± 0.44	−2.07 ± 0.64	0.53‖
Change in FEV_1 due to NIPPV ± SEM (% predicted value)	−5.33 ± 3.36	−7.75 ± 6.87	0.84‖
Change in linear decline of FEV_1 due to NIPPV ± SEM (% predicted/month)	+0.13 ± 0.18	+0.18 ± 0.34	0.93‖

*Two-sample t-test; †Fisher's exact test; ‡Log-rank test; §at first postintervention visit; ‖mixed effects model.

Table 2. Characteristics of spirometric measures, respiratory muscles strength, and arterial blood gases: rate of decline before and after noninvasive positive-pressure ventilation.

Feature	FVC (%)		FEV$_1$ (%)		MIP (%)		MEP (%)		Pco$_2$ (mmHg)		Po$_2$ (mmHg)	
	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P
Linear change per month	−2.31	0.0001	−2.09	0.0001	−0.13	0.81	−0.56	0.20	+0.20	0.28	−0.18	0.50
Quadratic change per month	+0.038	0.0001	+0.034	0.0001	+0.005	0.67	+0.010	0.21	−0.002	0.59	+0.001	0.83
Change due to initiation of NIPPV*	−2.48	0.39	−5.94	0.07	−6.33	0.11	−3.21	0.26	−0.34	0.76	−1.76	0.31
Change in linear rate of change due to NIPPV* (unit per month)	+0.10	0.52	+0.15	0.37	−0.02	0.93	+0.09	0.54	+0.02	0.76	+0.03	0.75

*NIPPV = noninvasive positive-pressure ventilation.

the rate of decline with time (Fig. 1, Table 2). The linear rates of decline of FVC and FEV$_1$ were 2.31 and 2.09 percent-predicted points per month, respectively ($P < 0.001$ for both), and were not significantly changed after initiation of NIPPV (Table 2). For instance, the rates of decline of FVC and FEV$_1$ slowed only by 0.1 and 0.15 percent-predicted points per month, respectively ($P > 0.2$ for both). No significant change in maximal inspiratory or expiratory pressures, Po$_2$, or Pco$_2$ was seen with time (Table 2).

Quality of life data pre- and postintervention was available in 8 patients, with results shown in Table 3. Despite increasing dyspnea scores, there was an im-

FIGURE 1. Plot of decline of FEV$_1$ percent-predicted with time. Continuous line shows the time course of FEV$_1$ expressed as percent of predicted value for the group as a whole. A quadratic trend has been incorporated in the graph. The break in the continuous curve represents the average drop in FEV$_1$ noted after initiation of noninvasive positive-pressure ventilation (with a median interval of 42 days between the start of intervention and first subsequent measurement). For graphical representation purposes, this has been selected to occur at around day 360, the median time of initiation of NIPPV. Dashed line represents projected decline without noninvasive ventilation.

provement in fatigue score and a trend toward improved mastery scores. In addition, the magnitude of change pre- and post-NIPPV reached the clinical significance threshold, as defined in the Materials and Methods section, for the fatigue and mastery scores (Table 3).

The patients used NIPPV for a median period of 42 days between initiation of intervention and the first postintervention measurements. Following that period, NIPPV was associated with a drop of 5.94 percent-predicted points in FEV$_1$ ($P = 0.07$), and by a drop of 2.48 percent-predicted points in FVC ($P = 0.39$) (Fig. 1 and Table 2). The intervention was also associated with a drop of 6.33 percent-predicted points in maximal inspiratory pressure ($P = 0.11$) (Table 2).

Complete data for immediate pre- and postintervention FVC, FEV$_1$, and maximal inspiratory and expiratory pressures, expressed as percent of predicted value, could be obtained for 28 patients. This subset of patients was similar to the group as a whole with respect to age, gender distribution, spirometric measures, and indices of respiratory muscle strength. However, a greater proportion of this subset was tolerant to NIPPV and, accordingly, had more hours of NIPPV use compared to the group as a whole (65.5% tolerance with mean of 6.5 h/day of NIPPV use in this subset vs. 48.9% tolerance with a mean of 5.9 h/day of NIPPV use for the overall group). The change of FVC% or FEV$_1$% between the start of the intervention and the first subsequent measurement was significantly correlated with the corresponding change in maximal inspiratory pressure percent (Pearson's correlation coefficient [r] = 0.39, $P = 0.04$ for FVC change; $r = 0.39$, $P = 0.04$ for FEV$_1$ change). After exclusion of two outliers from the data set, the correlation was only slightly improved ($r = 0.44$, $P = 0.03$ for FVC; $r = 0.49$, $P = 0.01$ for FEV$_1$) (Fig. 2).
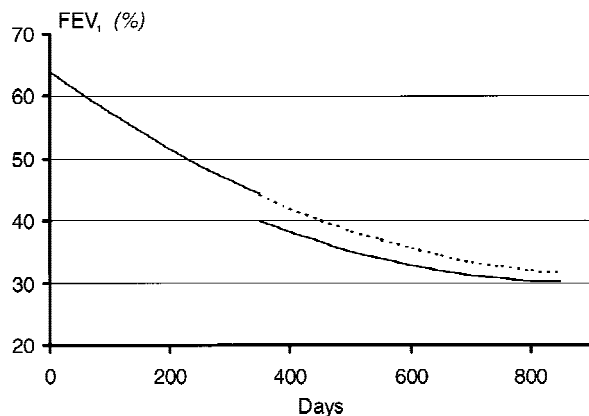
Table 3. Quality of life pre- and post-noninvasive positive-pressure ventilation in patients with amyotrophic lateral sclerosis.

Dimension	Pre-NIPPV	Post-NIPPV	Change required for clinical significance	P-value*
Mean dyspnea score ± SD	14.7 ± 3.8	12.6 ± 3.8	3.0	0.11
Mean fatigue score ± SD	11.1 ± 4.2	14.9 ± 4.7	2.0	0.03
Mean emotion score ± SD	30.9 ± 5.5	34.1 ± 6.3	4.0	0.16
Mean mastery score ± SD	16.8 ± 4.9	19.2 ± 2.6	2.0	0.07

Wilcoxon signed-rank test for comparison of medians.

No significant correlation was found with change in maximal expiratory pressure ($r = 0.30$, $P = 0.11$ for FVC; and $r = 0.19$, $P = 0.35$ for FEV_1). Multiple linear regression analysis revealed the magnitude of the change in FVC or FEV_1 pre- and postintervention was not correlated with the time lag between the start of intervention and the first measurement after initiation of NIPPV (data not shown).

DISCUSSION

Our study shows that NIPPV improves quality of life (particularly sense of fatigue and mastery over the disease) and survival, but does not slow the rate of decline of lung function nor does it improve daytime arterial blood gases or measures of respiratory muscle strength (MIP and MEP) in patients with amyotrophic lateral sclerosis. Moreover, initiation of NIPPV is associated with a trend toward a drop in FEV_1 and in maximal inspiratory pressure, with the magnitude of the change in FEV_1 (and FVC) pre- and post-NIPPV correlating with the corresponding change in maximal inspiratory pressure.

Although we demonstrated a strong linear rate of decline of spirometric function, this decline was not slowed by NIPPV, in contrast to results of other studies in patients with Duchenne muscular dystrophy or amyotrophic lateral sclerosis.[16,22,25] In a large retrospective study of patients with amyotrophic lateral sclerosis, Kleopa et al. reported a trend toward a slower rate of decline of lung function only in the subgroup of patients who used NIPPV for more than 4 h/day.[16] However, the minimal changes in the rate of decline of lung function noted in our study after initiation of NIPPV are unlikely to be of clinical significance. Taken together, these studies cast doubt on the ability of NIPPV to alter the course of progression of respiratory failure in amyotrophic lateral sclerosis.

The lack of a beneficial effect of NIPPV on arterial blood gases during unassisted breathing in our study also appears to contrast with other reports in patients with hypercapnic respiratory failure.[8,9] Because our population included only ALS patients, who typically have a more rapidly progressive course,

the lack of improvement in blood gases with NIPPV in our study may simply reflect the severity of the disease.

Despite high variability and effort dependence in measurements of respiratory muscle strength, our study suggests a drop in both maximal inspiratory pressure and FEV_1 after a median period of 42 days on NIPPV. Because lung volumes tend to fall with increasing inspiratory muscle weakness,[17,23] we sought to better determine the relationship between those two independently measured variables. As shown in Figure 2, the change in FVC or FEV_1 correlated with the change in maximal inspiratory pressures, thereby implying a cause–effect relationship. We therefore speculate that unloading of the inspiratory muscles by NIPPV may decondition this group of muscles and translate into decreases in maximal inspiratory pressures and measures of lung volumes. Factors that may have predisposed our patients to deconditioning include preexisting denervation of respiratory muscles due to the underlying pathology, and malnutrition to which patients with amyotrophic lateral sclerosis are at risk.[15,18] Alternative explanations such as incomplete adaptation and disruption of sleep by the device do not fully explain these results because our data show no significant difference between tolerant and intolerant groups in the magnitude of FEV_1 drop after NIPPV (Table 1).

As noted in Table 2, the trend for a negative effect of the intervention on spirometric measures was apparently limited to the FEV_1 (-5.94%, $P = 0.07$) and not the FVC (-2.48 decrease, $P > 0.20$). Technical difficulties and limitations in the measurement of FVC in patients at advanced stages of their disease may have affected the results. For instance, 60% of our patients were unable to achieve an expiratory time of 6 s or greater on the spirometric maneuver, indicating that end-of-test criteria were not met in many cases, resulting in underestimation of the FVC.[2] Furthermore, there was slightly better reproducibility of the FEV_1 than the FVC determinations (68% vs. 62%, respectively). These end-of-test and reliability concerns raise the question of whether the FEV_1 is a better determinant of disease severity
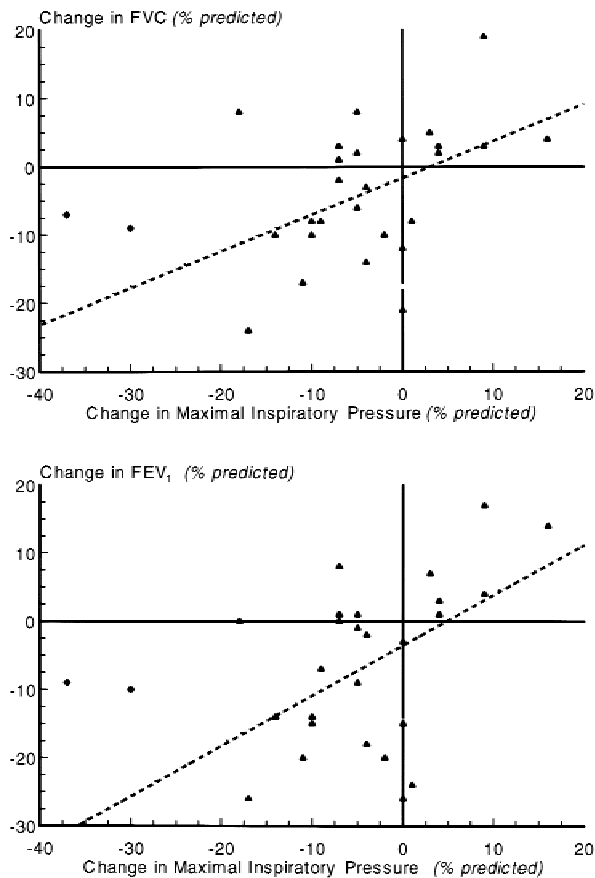
FIGURE 2. Plot of change in FVC percent-predicted **(top)** or FEV_1 percent-predicted **(bottom)** versus change in percent-predicted maximal inspiratory pressures before and after initiation of noninvasive positive-pressure ventilation. Change represents immediate postintervention minus immediate preintervention values. Dashed line is the regression line for the data points represented by triangles. The two diamond-shaped data points represent outliers excluded from the data in deriving the regression line. Their inclusion does not affect statistical significance or conclusions. Change in FVC = 0.54 · change in MIP – 1.7; Pearson's correlation coefficient $r = 0.44$, $P = 0.03$. Change in $FEV_1 = 0.74$ · change in MIP – 3.6; $r = 0.49$, $P = 0.01$.

or progression in restrictive pulmonary diseases such as amyotrophic lateral sclerosis.

Because the rate of decline is not significantly improved by the intervention, and because of concerns regarding possible premature deconditioning or unloading of inspiratory muscles, the study does not provide support for early initiation of NIPPV. Other unidentified mechanisms may justify early initiation and therefore the optimal timing of intervention remains to be determined. The current American Academy of Neurology recommendation to initiate NIPPV counseling for respiratory symptoms or for FVC < 50% is supported by our study because we demonstrated survival and quality-of-life benefits

when NIPPV was initiated at FVC% values that closely approximate this cutoff.[19]

Our study also suggests that the beneficial effects of NIPPV on quality of life (particularly fatigue score and mastery over the disease) and survival cannot be readily ascribed to increased respiratory muscle strength, improved daytime blood gases, or slowing of rate of decline of lung function. This interpretation accords with the work of Hill and colleagues, who attributed the efficacy of NIPPV to improvement in nocturnal ventilation rather than respiratory muscle rest.[12]

The potentially deleterious effects of NIPPV on spirometric measures and indices of inspiratory muscle strength therefore do not appear to translate into clinically definable sequelae in amyotrophic lateral sclerosis. However, this deleterious effect may be uncovered in more slowly progressive neuromuscular disorders, and perhaps account for the actuarial survival *disadvantage* reported with NIPPV in patients with Duchenne muscular dystrophy.[21] In addition, this putative deconditioning mechanism may foster rapid dependence on NIPPV, and explain anecdotal reports of rapidly increasing reliance on NIPPV once started. For instance, it has been our experience, and that of others, that tolerant patients progressively increase their time on NIPPV up to 24 h/day.[6] Whether this reflects effective palliation of symptoms or accelerated dependence on the device is unclear.

Our results must be interpreted with caution because our patients were predominantly older men with signs and symptoms of respiratory insufficiency at initiation of NIPPV, thereby possibly limiting the applicability of our results to other patients with amyotrophic lateral sclerosis. The quality-of-life scale we used may be inadequate for amyotrophic lateral sclerosis, and the data we presented were derived from a small number of patients. We found the dyspnea dimension particularly difficult to apply, as it refers to types of activity patients with amyotrophic lateral sclerosis would be unable to perform at such an advanced stage of their disease. Finally, because our data represent average results for the aggregate of our patients, individual variations were obscured. For instance, some of our patients had an improved rate of decline of lung function and improved indices of respiratory muscle strength after NIPPV. This variability is exemplified in Figure 2, which shows that a substantial number of patients had increases in maximal inspiratory pressures and FVC or FEV_1 after initiation of NIPPV. We were unable to identify potential positive responders by stratifying patients on the basis of FVC at initiation of NIPPV, tolerance of device, absence of bulbar symptoms, age, or gen-

der (data not shown). Studies specifically designed to address the impact of the unloading effect of NIPPV on respiratory muscle function are required.

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