Noninvasive ventilation in ALS

Indications and effect on quality of life

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Abstract—*Background:* Noninvasive ventilation (NIV) probably improves survival in ALS, but the magnitude and duration of any improvement in quality of life (QoL) and the optimal criteria for initiating treatment are unclear. *Methods:* QoL (Short Form-36 [SF-36], Chronic Respiratory Disease Questionnaire, Sleep Apnea Quality of Life Index) and respiratory function were assessed every 2 months and polysomnography every 4 months in 22 subjects with ALS. A trial of NIV was offered when subjects met one or more predefined criteria: orthopnea, daytime sleepiness, unrefreshing sleep, daytime hypercapnia, nocturnal desaturation, or an apnea–hypopnea index (AHI) of >10. Seventeen subjects were offered a trial of NIV; 15 accepted, and 10 continued treatment subsequently. Outcome was assessed by changes in QoL and NIV compliance (h/day). Subjects were followed to death or for at least 26 months. *Results:* QoL domains assessing sleep-related problems and mental health improved (effect sizes 0.88 to 1.77, $p < 0.05$) and were maintained for 252 to 458 days. Median survival following successful initiation of NIV was 512 days, and survival and duration of QoL benefit were strongly related to NIV compliance. Vital capacity declined more slowly following initiation of NIV. Orthopnea was the best predictor of benefit from, and compliance with, NIV. Daytime hypercapnia and nocturnal desaturation also predicted benefit but were less sensitive. Sleep-related symptoms were less specific, and AHI > 10 was unhelpful. Moderate or severe bulbar weakness was associated with lower compliance and less improvement in QoL. *Conclusions:* NIV use was associated with improved QoL and survival. Subjects with orthopnea and preserved bulbar function showed the largest benefit.

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Respiratory muscle weakness is present in most patients with ALS at diagnosis[1,2] and is a strong independent predictor of quality of life (QoL).[1] It causes breathlessness and, as a consequence of hypoventilation and sleep disruption, morning headache, unrefreshing sleep, daytime sleepiness, lethargy, fatigue, poor concentration, and poor appetite. Death is usually due to respiratory failure, typically within 2 to 3 years of diagnosis, and respiratory function is the best predictor of survival.[3,4]

Domiciliary noninvasive ventilation (NIV) probably improves survival in ALS,[5-7] but its impact on QoL is less clear,[7,8] and the optimal criteria for initiating treatment are uncertain. The point prevalence of NIV use in ALS has been estimated at 2 to 4% of all patients in the UK[9] and 7 to 15% in selected populations in the USA.[10,11] There is marked variation in clinical practice in both countries,[9,11] probably because many physicians are anxious that NIV may merely prolong suffering in a distressing and fatal disease.

We performed a prospective study of the impact of NIV on QoL in ALS, with the aims of establishing 1) the magnitude of any benefit in QoL and which instruments are most useful for its recognition; 2) the duration of any improvement in QoL; 3) the optimal criteria for initiating NIV; and 4) the influence of bulbar involvement on outcome.

Methods. *Subjects.* All subjects had definite or probable ALS (El Escorial criteria). Patients with life-threatening co-existing disease, inability to communicate, or aged over 75 years were excluded. Of 25 patients who were eligible, 22 agreed to participate in the trial. Of these, 15 were recruited within 3 months of diagnosis, and 7 were referred because of declining respiratory function or respiratory or sleep-related symptoms. One subject later withdrew owing to difficulty traveling to the center. Ethical approval for the study was obtained, and each subject gave informed consent.

Investigations. Subjects were assessed periodically following enrollment. A trial of NIV was offered subsequently, if and when the predefined criteria (see below) were satisfied during the first year of the trial. Respiratory muscle function was assessed every 2 months by measurement of vital capacity (VC)[12] both sitting and supine, maximum static inspiratory (P_I max) and expiratory (P_E max) pressures,[2,13] and sniff nasal inspiratory pressure (SNIP).[13] VC was measured using a dry wedge spirometer (Vitalograph, Buckinghamshire, UK). P_I max, P_E max, and SNIP were measured using a handheld meter (Precision Medical, N. Yorkshire, UK). To overcome mouth leaks, an adapted anesthetic full facemask was used in subjects with facial muscle weakness. Measurements are expressed as percentage of predicted.[14-16] Daytime arterial blood gases while breathing room air were also measured.

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Table 1 *Subject characteristics on recruitment and on initiation of NIV*

Characteristics	Data at recruitment		Data when criteria for NIV satisfied
	Recent diagnosis	Referred with symptoms	
Demographics			
N	15	7	17
Age (range), y	57.8 (32–74)	59.3 (48–73)	61.8 (48–74)
Male/female	10/5	5/2	12/5
Bulbar weakness, %	33	43	41
Disease duration,* mo	15.2 (9.9)	54.0 (35.0)	32.5 (29.0)
Respiratory function			
VC, % predicted	88.0 (21.9)	36.0 (11.7)	59.4 (29.7)
Fall VC supine, % fall	8.8 (9.8)	23.7 (22.8)	18.3 (18.6)
P_I max, % predicted	77.6 (31.0)	23.2 (3.5)	46.2 (34.7)
P_E max, % predicted	65.6 (30.0)	24.0 (7.9)	39.5 (33.3)
SNIP, % predicted	65.5 (30.5)	20.9 (7.7)	38.2 (25.5)
Median P_aCO_2 (range), kPa	5.38 (4.59–5.7)	7.00 (5.74–15.1)	5.54 (4.59–15.1)
Polysomnography			
Mean S_aO_2, %	95.8 (1.2)	92.0 (1.8)	94.0 (2.2)
Median % time $S_aO_2 < 90\%$ (range)	0 (0–3.7)	13.3 (0–41.4)	0.6 (0–41.4)
Total sleep time, min	283 (73)	149 (48)	203 (73)
Stage 1 sleep, %	21.2 (12.1)	36.6 (12.5)	32.3 (13.6)
REM, %	15.2 (5.6)	4.8 (7.0)	9.8 (8.2)
Median AHI (range)	5.6 (0.8–55.4)	12.3 (0.3–47.4)	7.7 (0–55.4)
Symptoms			
Orthopnea	1/15	7/7	11/17
Unrefreshing sleep	4/15	7/7	13/17
Daytime sleepiness	0/15	4/7	5/17
Morning headache	3/15	4/7	7/17

Findings in recently diagnosed subjects and those referred because of symptoms or declining lung function at recruitment and separately for all subjects offered a trial of noninvasive ventilation (NIV) at the time they satisfied one or more criteria. Results are means (SD) unless otherwise indicated.

* Disease duration: from onset of weakness. VC = vital capacity; P_I max = maximum inspiratory pressure; P_E max = maximum expiratory pressure; SNIP = sniff nasal inspiratory pressure; AHI = apnea–hypopnea index.

Polysomnography was performed in the hospital every 4 months. Sleep stage, arousals, apneas, and hypopneas were scored manually by standard criteria.[17-19] The apnea–hypopnea index (AHI) was calculated as number of events per hour of sleep. Mean and nadir oxygen saturation (S_aO_2) and the proportion of time spent with $S_aO_2 < 90\%$ were determined.

QoL was assessed every 2 months using the following generic and specific instruments:

1. The Short Form-36 (SF-36; UK version)[20] is a widely used generic QoL instrument and is reliable, valid, and responsive in ALS.[21] It assesses eight domains of QoL (table 2) plus one item on change in health. In addition, two summary scores may be calculated, the Mental Component Summary (MCS) and the Physical Component Summary.
2. To assess the consequences of respiratory compromise, we used the Chronic Respiratory Disease Questionnaire (CRQ).[22] Dyspnea is assessed on activities identified by the subject, a point of importance in ALS as the pattern of disability varies considerably between subjects. The CRQ has been used successfully in other conditions causing respiratory failure.[23]
3. To assess the effects of sleep disturbance, we used the Sleep Apnea Quality of Life Index (SAQLI)[24] and a symptom scale, the Epworth Sleepiness Scale (ESS).[25] The SAQLI was developed to assess QoL in patients with obstructive sleep apnea. Its Symptoms domain uses symptoms identified as important by the subject. The SAQLI also assesses any side effects of treatment. The ESS is a simple self-administered questionnaire assessing daytime sleepiness.

Limb and axial muscle strength was assessed using a muscle score calculated by adding together the MRC clinical scale scores for 22 muscle groups (maximum = 110).[26] Functional status was assessed using the disease-specific ALS Functional Rating Scale (ALSFRS).[27] Bulbar function was assessed on a 0- to 6-point scale.

The criteria for offering a trial of NIV were determined a priori as any of the following:

1. Orthopnea, defined as breathlessness when supine, attributable to respiratory muscle weakness after exclusion of other potential causes.
2. Daytime sleepiness (ESS > 10) or unrefreshing sleep in the presence of sleep-disordered breathing[19] or respiratory muscle weakness (P_I max and SNIP <80% predicted).
3. Daytime $P_aCO_2 > 45$ mm Hg.

Table 2 *Magnitude and duration of quality-of-life benefit with noninvasive ventilation*

Instrument	Domain	Effect size	*p*	Median duration of beneficial effect, d
SF-36	Physical Function	0.02	NS	0
	Role Physical	0.53	NS	55
	Role Emotional	0.93	0.023	239
	Social Function	0.37	NS	231
	Mental Health	1.16	0.027	458
	Energy Vitality	0.71	NS	221
	Pain	0.15	NS	151
	General Health Perception	0.13	NS	134
	PCS	−0.62*	0.0030	N/A
	MCS	1.74	0.0080	252
CRQ	Dyspnea	0.76	0.0036	416
	Fatigue	0.88	0.046	343
	Emotional Function	0.71	0.018	281
	Mastery	1.02	0.037	325
SAQLI	Daily Function	0.62	NS	232
	Social Isolation	0.96	0.024	368
	Emotional Function	0.59	NS	169
	Symptoms	1.77	0.0022	369
	Score	1.11	0.034	289
ESS		1.04	0.034	401
ALSFRS		−0.80*	0.0006	N/A

Effect size (mean difference/SD) of the peak improvement in quality of life (QoL) on noninvasive ventilation compared with baseline and the median period QoL is maintained at or above baseline for all domains of QoL and the ALS Functional Rating Scale (ALSFRS). Effect size is the mean number of standard deviations a measure changes by and is classified as small = 0.2–0.49, moderate = 0.5–0.79, and large ≥0.8.

* Overall the SF-36 PCS and ALSFRS deteriorated; any improvement in individual subjects was short lived (median duration at or above baseline: SF-36 PCS = 34 d, ALSFRS = 0 d).

SF-36 = Short Form-36; PCS = Physical Component Summary; MCS = Mental Component Summary; CRQ = Chronic Respiratory Disease Questionnaire; SAQLI = Sleep Apnea Quality of Life Index; ESS = Epworth Sleepiness Scale.

4. Nocturnal desaturation (defined as $S_aO_2 < 90\%$ for ≥5% of the night).
5. AHI > 10 events/h of sleep.

NIV was established in the hospital using a ResMed VPAP STII pressure-support ventilator in spontaneous/timed mode (ResMed Ltd., Abingdon, UK). Inspiratory (IPAP) and expiratory (EPAP) positive airway pressures were adjusted according to nocturnal oximetry, daytime arterial blood gases, and compliance (mean IPAP = 16 cm H_2O, EPAP = 4 cm H_2O). Rise time, $IPAP_{max}$ (maximum duration of IPAP), and $IPAP_{min}$ (minimum duration of IPAP) were adjusted to achieve optimal comfort and efficiency of ventilation. Interfaces used included nasal, oronasal, and total facemasks and mouthpieces (ResMed; Respironics, Bognor Regis, UK; and Puritan Bennett, Bicester, UK). Most subjects with bulbar and facial muscle weakness required an oronasal or total facemask. Ventilator asynchrony, usually due to persisting air leaks, was corrected by limiting inspiratory time ($IPAP_{max}$). All subjects were taught assisted cough techniques by an experienced respiratory physiotherapist, tailored to their bulbar and expiratory muscle function. After initiation of NIV, QoL, lung function, and compliance with treatment were assessed at 1 and 3 months and then at two monthly intervals thereafter in the outpatient clinic or the patient's home. NIV compliance was defined as the average number of hours per 24 hours that the subject was breathing through the ventilator (i.e., "mask on" time) and was recorded automatically by the ventilator. All subjects were followed to death or for at least 26 months following initiation of NIV.

Analysis. The responses of each domain of QoL were compared in terms of the effect size (mean difference/SD) of the maximum change compared with the value at initiation of NIV in subjects continuing NIV after the initial trial (efficacy analysis). Effect size is the mean number of standard deviations a measure changes by and is classified as follows: small = 0.2 to 0.49, moderate = 0.5 to 0.79, large ≥ 0.8.[28] The significance of changes in QoL compared with pretreatment was assessed by paired *t*-test. The period over which QoL was maintained at or above the pretreatment level was also calculated

The criteria for initiating NIV were compared by intention-to-treat analysis using 1) effect sizes for the SF-36 MCS and Symptoms domain of the SAQLI (the indices showing the greatest improvement in the efficacy analysis) at 1 month to minimize any bias due to a survivor effect; and 2) NIV compliance over the total treatment period (in subjects who were intolerant of, or declined, NIV, compliance during the trial period was calculated).

The outcome for subjects with moderate or severe bulbar impairment compared with those with normal function or mild weakness was similarly assessed by the changes in the SF-36 MCS and SAQLI Symptoms domain at 1 month and NIV compliance. To eliminate the influence of different criteria for initiating NIV, this comparison was restricted to subjects established on NIV for orthopnea (the largest group).

Relations between 1) survival and 2) duration of QoL benefit

and each of compliance, age, gender, P_I max, P_aCO_2, bulbar score, and limb and axial muscle score were evaluated by univariate and multivariate analysis. Relations between compliance and subject characteristics at initiation of NIV were also assessed. To eliminate the effects of differences in the timing of initiation of NIV, this analysis was also limited to the orthopnea group.

Results. Of the 22 subjects recruited, 17 met one or more criteria for initiation of NIV during the period of the study. Fifteen accepted a trial, and 10 continued treatment subsequently. Overall, NIV was more difficult to establish in subjects with moderate or severe bulbar impairment. The characteristics of the 17 subjects at the time they satisfied one or more of the criteria for NIV are shown in table 1. Polysomnography data were not available in one subject.

Responsiveness to NIV of QoL domains and duration of benefit. Large or very large improvements were seen in the ESS, SF-36 (Mental Health and Emotional Limitation domains and MCS), CRQ (Fatigue and Mastery domains), and SAQLI (Social Isolation and Symptom domains, summary score). The CRQ Dyspnea and Emotional Function domains showed moderate improvements. The SF-36 Energy Vitality domain showed a trend for a moderate improvement overall and a large improvement in the nine subjects with orthopnea (effect size = 1.13, $p = 0.035$). For most domains of QoL, the peak improvement in QoL was seen 3 to 5 months after starting treatment (figure). Responsive domains of QoL were maintained at or above baseline for most of the period of follow-up and survival (median duration for individual domains 252 to 458 days). In contrast, the ALSFRS and domains of QoL assessing physical function declined in all subjects, reflecting disease progression. In general, domains with the largest effect sizes showed more sustained improvements. The largest improvements were in the SF-36 MCS and SAQLI Symptoms domain, and these two indices were therefore chosen to compare the different criteria for initiating NIV (table 2).

Survival following initiation of NIV. Median (range) survival of the 10 subjects who elected to continue NIV was 512 (191 to 793) days. To date, 9 of these 10 subjects have died: Five died during an acute respiratory infection and four because of disease progression. Of these, three elected to discontinue NIV shortly before death.

Among subjects with orthopnea, median survival of the nine subjects who complied with NIV was longer than that of the two who declined or were intolerant of NIV (488 vs 28 days; log rank, $p = 0.0004$).

Influence of NIV on lung function. The median rate of decline in VC following initiation of NIV was slower than before treatment (pre 2.52 vs post 1.09% predicted/month; sign test, $p = 0.039$). There was no evidence of an early detrimental effect of NIV on VC; mean VC immediately prior to initiation of NIV was 48.3% predicted, and after 1 month of treatment, it was 47.2% predicted.

Criteria for initiating NIV. For the 17 subjects who met the criteria for NIV, the effect sizes of changes in SF-36 MCS and SAQLI Symptoms domain at 1 month and mean compliance with NIV over the treatment period are shown in relation to each indication in table 3. At the time they qualified for a trial, six satisfied only one criterion, five satisfied two criteria, and six satisfied more than two criteria. Results for five orthopneic patients who had a normal daytime P_aCO_2 are shown separately. It was noteworthy that 9 of the 11 subjects with orthopnea continued using NIV after the initial trial, with a large improvement in QoL and excellent compliance.

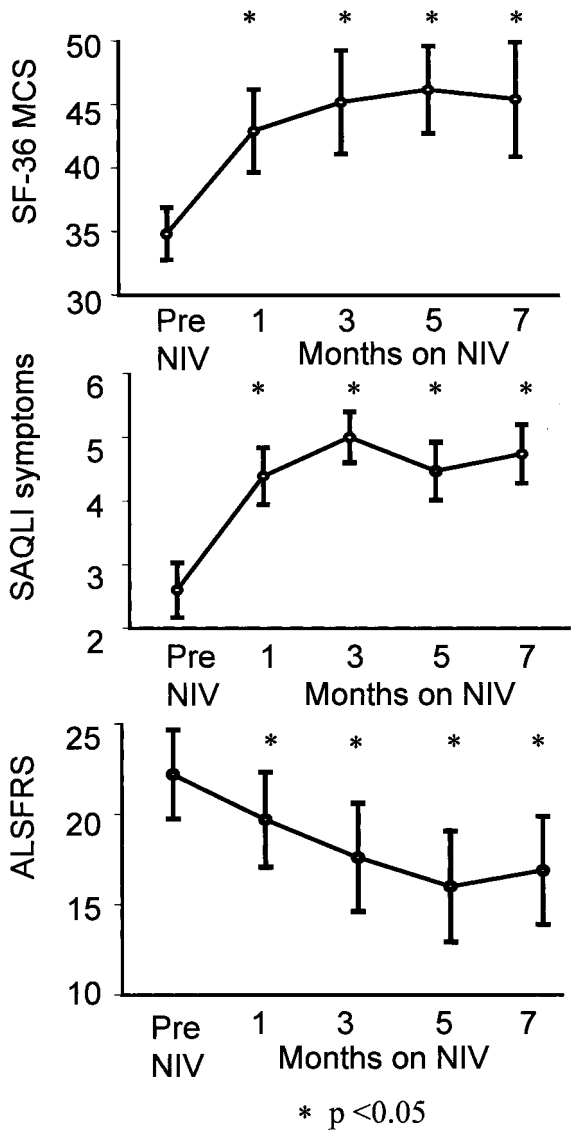

Figure. Serial data for the Short Form-36 Mental Component Summary (SF-36 MCS), Sleep Apnea Quality of Life Index (SAQLI) Symptoms domain, and ALS Functional Rating Scale (ALSFRS) immediately before starting noninvasive ventilation (NIV) and at 1, 3, 5, and 7 months on NIV. The slight improvement in the ALSFRS score at 7 months is due to a survivor effect.

Of 13 subjects with unrefreshing sleep or daytime sleepiness (ESS > 10), 12 accepted a trial of NIV and 9 continued NIV after the initial trial. Compliance was good, but benefit was less than in those with orthopnea. Two of these subjects had a trial for sleep symptoms only; despite significant respiratory muscle and bulbar weakness, both discontinued treatment because of lack of benefit.

All subjects with nocturnal desaturation also had daytime hypercapnia, and results for these criteria are therefore combined. All also had orthopnea, but, of note, the blood gas criteria failed to identify four other normocapnic subjects with orthopnea who continued NIV with benefit.

AHI was unhelpful as a guide to treatment; four of the seven subjects with an AHI of >10 had a trial for this

Table 3 *Criteria for initiating NIV: QoL and compliance*

Criteria for NIV	n	Continued Rx	Compliance, h/d	SAQLI Symptoms effect size	SF-36 MCS effect size
Orthopnea	11 (0)	9	8.0	2.89	1.40
Orthopnea with normal P_aCO_2	5 (0)	4	7.0	3.29	1.23
Sleep-related symptoms	13 (2)	9 (0)	7.2 (1.7)	1.26 (0.00)	0.87 (0.16)
$P_aCO_2 \uparrow$, $S_aO_2 \downarrow$	6 (0)	5	8.7	2.75	1.60
AHI > 10	7 (4)	3 (1)	3.4 (1.4)	0.34 (−0.26)	0.34 (0.24)

Acceptability of and compliance with noninvasive ventilation (NIV) and effect size of the improvement in the Sleep Apnea Quality of Life Index (SAQLI) Symptoms domain and Short Form-36 (SF-36) Mental Component Summary (MCS) at 1 month are shown for each criterion for initiating treatment and for the subgroup with orthopnea but normal daytime P_aCO_2 (intention-to-treat analysis). Most subjects satisfied more than one criterion and results for subjects meeting only the stated criterion are in parentheses.

AHI = apnea–hypopnea index.

criterion alone, but only one continued using NIV, with poor compliance and no improvement in QoL.

Compared with subjects with normal or only mildly impaired bulbar function, those with moderate or severe bulbar involvement showed lower mean compliance (moderate or severe impairment = 4.9 h/day, normal or mild impairment = 9.1 h/day) and QoL benefit (effect size SAQLI Symptoms domain: moderate or severe impairment = 1.85, normal or mild impairment = 3.28).

Predictors of survival, QoL benefit, and NIV compliance. Duration of survival correlated with NIV compliance (r = 0.70, p = 0.016) only. In univariate analysis, duration of QoL benefit (SF-36 MCS) correlated with compliance (r = 0.86, $p < 0.001$) and age($r = -0.61$, p = 0.048). However, in multivariate analysis, compliance was the only independent predictor of QoL benefit.

In univariate analysis, NIV compliance correlated with age($r = -0.62$, p = 0.042) and upper limb muscle score (r = 0.67, $p < 0.05$) and showed a trend toward correlation with ALSFRS bulbar score (r = 0.58, p = 0.06) and P_I max ($r = -0.56$, p = 0.07). In multivariate analysis, the only independent predictors of compliance were age and upper limb muscle score (adjusted r^2 = 0.76).

Discussion. We showed a large and sustained improvement in QoL following initiation of NIV. Furthermore, subjects with orthopnea but normal daytime P_aCO_2 and no nocturnal desaturation improved to a similar extent as those with hypercapnia or desaturation, suggesting that reliance on such measurements may deprive many patients of potential benefit (see table 3). Domains of QoL reflecting sleep disruption and mental health (SAQLI Symptoms, SF-36 Mental Health and MCS, and CRQ Fatigue) showed the greatest improvements, which were maintained for a median of 252 to 458 days and for most of the duration of both follow-up and survival, despite disease progression (see table 2). A sustained improvement in the SF-36 Mental Health domain following initiation of NIV in 8 subjects with ALS has previously been reported,[29] but a subsequent study of 16 subjects showed improvement only in the SF-36 Energy Vitality domain (results for the MCS were not reported in these studies).[8] Compared with the latter study, we found similar improvements in the Energy Vitality domain in subjects with orthopnea and hypercapnia, in addition to the domains cited above. In a further study of eight subjects, the Mastery and Fatigue domains of the CRQ improved following initiation of NIV[30] and were the most responsive domains of the CRQ in our study.

Median (range) survival from initiation of NIV of subjects who continued treatment in our study was 512 (191 to 793) days, which compares favorably with previous studies. Survival following initiation of NIV was longer than in the most recent UK study,[8] both overall and in our subgroup offered NIV for established respiratory failure (day $P_aCO_2 > 45$ mm Hg). Factors that may be relevant to the difference between these two studies include possible differences in the population studied, ventilators used, and compliance with treatment. In common with our findings, survival has previously been shown to be strongly related to NIV compliance.[6,30] The ventilator we employed has certain features ($IPAP_{min}$, $IPAP_{max}$, and "smart on/off mode") that may improve compliance. Also, EPAP, not available with some machines, improves oxygenation in patients with muscle weakness.[31] The frequency of review, range of interfaces available, and level of medical, family, and social support in the trial setting may also influence compliance and consequently survival.

All subjects who elected to continue NIV after the initial trial were cared for in their own homes for most of the subsequent period of survival, but most died in the hospital, frequently with evidence of an acute respiratory infection. Three subjects elected to discontinue NIV, and in each, this was achieved without undue distress for the patient or the family, using appropriate alternative palliative therapy. The option of tracheostomy was discussed with subjects once they began to require additional daytime NIV support, but all declined.

A recent study of the effects of NIV on lung function in 47 subjects reported that NIV was associated with a fall in VC, with an apparent "step" change in the graph of VC over time at initiation of NIV, but no

change in the rate of decline.[30] The estimation of the rate of decline in VC on NIV was, however, based on a mean of only 1.9 measurements. Data on subjects who declined NIV were not provided, but the graph of VC vs time pre NIV was extrapolated to estimate VC had NIV not been commenced. This suggested that if subjects were not treated with NIV, VC would decline more slowly as disease advanced, in contrast to the findings of an earlier study of the natural history of VC over time in motor neuron disease.[12] We found that initiation of NIV was associated with a slower decline in VC, with no evidence of an early detrimental effect of NIV on VC. Our findings support the results of a larger retrospective study (n = 122)[6] in which subjects who complied with NIV showed a slower decline in VC than those who declined treatment. Although there was a "step" in the graph of VC over time at the point of intersection of lines of best fit before and during NIV, similar to the study described above, a similar and larger change was seen in subjects who declined NIV compared with those who complied, suggesting that this "step change" in VC may be an artifact of data modeling.

Orthopnea was the best predictor of compliance with, and benefit from, NIV. Nine of 10 subjects who continued NIV with improvement in QoL had orthopnea; of these, 4 had normal daytime P_aCO_2 and maintained nocturnal oxygen saturation >90% prior to treatment. Orthopnea was associated with substantial sleep disruption, frequent arousals, reduced total sleep time, and reduced or absent REM sleep, even in the absence of desaturation or daytime hypercapnia (data not shown). Subjects with diaphragmatic weakness are predisposed to oxygen desaturation during sleep, particularly REM sleep,[32,33] and may sacrifice sleep quality to maintain adequate ventilation. Orthopnea was strongly associated with sleep-related symptoms, but these may be underreported or attributed to the underlying disease. In subjects with bulbar involvement, it is important to distinguish orthopnea from choking on secretions. A retrospective study of 27 patients compliant with NIV reported that orthopnea was the most common symptom present at initiation of treatment, supporting our findings. Details of patients who were intolerant of, or declined, NIV were not given.[34]

Sleep-related symptoms were sensitive but less specific predictors of sustained benefit from NIV and consequently were associated with poorer compliance and improvement in QOL. Sleep disruption is common in ALS, due not only to respiratory muscle weakness but also to discomfort due to inability to turn, choking on secretions, anxiety, and depression. Compared with orthopnea, sleep-related symptoms did not identify any additional subjects who benefited from NIV.

Both daytime hypercapnia and nocturnal desaturation were associated with a large benefit from, and excellent compliance with, NIV. However, all subjects with these features also had orthopnea, and these criteria failed to identify four who continued NIV with benefit. The longer average use of subjects with daytime hypercapnia reflects the greater requirement for ventilatory support with established respiratory failure.

One of the subjects with AHI of >10 who continued treatment had predominantly obstructive events with no other criteria for treatment, and continuous positive airway pressure might have been equally effective. The other three subjects with AHI of >10 and no other criteria did not continue NIV owing to lack of perceived benefit.

Regular assessment of nocturnal oxygen saturation has been recommended to guide initiation of NIV in ALS, but our subjects with orthopnea benefited from NIV even without nocturnal desaturation, suggesting that routine nocturnal studies without relevant symptoms are unnecessary and potentially misleading. It is likely that application of NIV in this situation controls symptoms by improving sleep architecture.

Some studies have reported a poor outcome in patients with bulbar disease,[5,33] whereas others have reported successful treatment despite bulbar impairment.[6] We found moderate or severe bulbar involvement was associated with lower compliance and less improvement in QOL, but the response was still clinically useful.

We have compared the outcome following initiation of NIV for different criteria, but we did not randomize subjects to NIV or no treatment/sham ventilation. Subjects who declined or were intolerant of NIV may not be representative of the general ALS population. Therefore, we have not assessed the natural history of QoL or survival without ventilatory support or the placebo effect of sham ventilation.

The SF-36 is the only QoL instrument previously validated in subjects with ALS. We have assessed the validity, reliability, test–retest stability, and response to disease severity and treatment with NIV of several QoL instruments including the SF-36, CRQ, and SAQLI, and a symptom scale, the ESS. The results support the use of these instruments to assess the impact of NIV on QoL in ALS and have been submitted for publication.

The protocol for our study was very demanding, and it is possible that unintentionally this selected a group of patients who were more motivated to succeed with NIV than others who were unwilling to participate. The relatively small number of subjects may limit the applicability of our results to the total population with ALS. To address these issues, we are currently undertaking a larger randomized controlled trial of the effects of NIV on QoL.

The successful clinical application of NIV in patients with ALS, particularly if bulbar function is impaired, requires careful attention to detail in the clinical management of problems such as excess saliva and in the choice of the interface, ventilator, and ventilator settings. Regular review is important as the optimal interface and ventilator settings change with disease progression. Our results might not nec-

essarily be replicated in routine practice in this challenging group of patients.

Both age and upper limb muscle score at initiation of NIV were predictors of compliance, which in turn was the sole independent predictor of survival and QoL benefit. This suggests that younger patients with relatively preserved upper limb function, who consequently will be able to fit and remove their mask independently, are more likely to benefit from NIV. We found orthopnea due to respiratory muscle weakness to be the most useful criterion for initiating NIV. Compared with patients with normal or only mild bulbar impairment, those with moderate or severe impairment show less, although still clinically significant, benefit from NIV, but they present greater challenges in ventilation management. In contrast, early initiation of NIV for relatively asymptomatic impairment of respiratory function is associated with a high failure rate due to poor compliance both in our study and in other work.[6] More conventional criteria such as symptomatic daytime hypercapnia and nocturnal desaturation are associated with excellent compliance and improvement in QoL, but reliance on these criteria alone may deny beneficial treatment with NIV at an earlier stage. Furthermore, survival following the onset of established respiratory failure is usually short, possibly only a few weeks, leaving little time to initiate ventilatory support.

Our study confirms that NIV is an effective means of palliating symptoms and improving and maintaining QoL in selected patients with symptomatic respiratory compromise due to ALS. The sustained improvement in QoL suggests that NIV is not merely extending suffering.

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