Survival in Amyotrophic Lateral Sclerosis With Home Mechanical Ventilation

The Impact of Systematic Respiratory Assessment and Bulbar Involvement

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Study objectives: To analyze (1) the impact of a protocol of early respiratory evaluation of the indications for home mechanical ventilation (HMV) in patients with amyotrophic lateral sclerosis (ALS), and (2) the effects of the protocol and of bulbar involvement on the survival of patients receiving noninvasive ventilation (NIV).

Design and setting: Retrospective study in a tertiary care referral center.

Patients: HMV was indicated in 86 patients with ALS, with 22 patients (25%) presenting with intolerance to treatment associated with bulbar involvement. Treatment with HMV had been initiated in 15 of 64 patients prior to initiating the protocol (group A) and in the remaining 49 patients after protocol initiation (group B).

Results: In group A, the majority of patients began treatment with HMV during an acute episode requiring ICU admission ($p = 0.001$) and tracheal ventilation ($p = 0.025$), with a lower percentage of patients beginning HMV treatment without respiratory insufficiency ($p = 0.013$). No significant differences in survival rates were found between groups A and B among patients treated with NIV. Greater survival was observed in group B ($p = 0.03$) when patients with bulbar involvement were excluded (96%). Patients without bulbar involvement at the start of therapy with NIV presented a significantly better survival rate ($p = 0.03$). Multivariate analysis showed bulbar involvement to be an independent prognostic factor for survival (relative risk, 1.6; 95% confidence interval, 1.01 to 2.54; $p = 0.04$). No significant differences in survival were observed between patients with bulbar involvement following treatment with NIV and those with intolerance, except for the subgroup of patients who began NIV treatment with hypercapnia ($p = 0.0002$).

Conclusions: Early systematic respiratory evaluation in patients with ALS is necessary to improve the results of HMV. Further studies are required to confirm the benefits of NIV treatment in patients with bulbar involvement, especially in the early stages.

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Key words: amyotrophic lateral sclerosis; bulbar impairment; home mechanical ventilation; respiratory assessment

Abbreviations: ALS = amyotrophic lateral sclerosis; HMV = home mechanical ventilation; NIV = noninvasive ventilation; S1 = setting 1; S4 = setting 4

The most frequent cause of death in patients with amyotrophic lateral sclerosis (ALS) is respiratory insufficiency secondary to impairment of the respiratory musculature. Although some cases of acute respiratory insufficiency have been described as the first manifestation of the disease, impairment of the respiratory musculature generally appears in advanced phases. Thus, symptoms indicating respira-
tory involvement, such as effort dyspnea, or sleep disorders may not be recognized in the general context of the disease. Similarly, arterial blood gas level alterations appear very late in the respiratory progression, and respiratory involvement may at times only be diagnosed during an acute episode leading to death or long-term tracheal ventilation. Invasive tracheal ventilation, however, presents several problems, not only because of the high economic and social costs, but also because of the possibility of prolonged survival leading to undesirable situations associated with poorer quality of life.

In recent years, some studies have indicated that therapy with noninvasive ventilation (NIV) improves both the survival and the quality of life of these patients, suggesting early treatment initiation. One factor that may limit the efficacy of NIV and make patient adaptation and tolerance difficult is bulbar involvement, although its impact on the long-term evolution of the disease has yet to be evaluated.

Treatment with home mechanical ventilation (HMV) was initiated by the Hospital Universitari de Bellvitge, L’Hospitalet, Spain, in 1988, and since then it has been initiated in > 500 patients. In 1997, a protocol of early respiratory evaluation was implemented in ALS patients with the aim of improving disease management, from a respiratory perspective, allowing both anticipated decision making and early indication of NIV. The aims of this study were to evaluate the evolution of ALS patients treated with HMV, assessing the impact of an early respiratory evaluation protocol and the consequences of bulbar involvement at the time of treatment initiation.

Materials and Methods

A retrospective study was carried out from 1988 to December 2002 and included all patients in whom ALS had been diagnosed (according to standard criteria) and treatment with HMV was indicated.

A volume ventilator (LIFECARE PLV100; Respironics; Murrysville, PA) was used in all cases of invasive ventilation, whereas either a volume ventilator (LIFECARE PLV100; Respironics; and PV 501; BREAS Medical; Gothenburg, Sweden) or a bilevel pressure ventilator (BiPAP; Respironics; and Sullivan VPAP ST II; ResMed Ltd; Abingdon, UK) was used for NIV. Interfaces included nasal masks (customized or commercial) with a chinstrap (to minimize oral leaks), mouthpiece, or facemask. The choice of ventilator and interface was based on the adaptation of the patient and the number of hours of ventilation required. Treatment with HMV was initiated during a hospital admission, and ventilation parameters were adjusted to achieve comfort as well as adequate ventilation according to daytime arterial blood gas levels and nocturnal oximetry measurements. Patients with ineffective cough (ie, peak flow cough, < 250 L/min) were provided with a salivary aspirator, and the caregivers were trained in the use of assisted cough maneuvers and hyperinflation with a compressible ventilator bag or volume ventilator.

Respiratory Evaluation Protocol

Until 1997, ALS patients were evaluated in the Department of Pneumology on request by the Department of Neurology, generally when respiratory symptoms were evident with hypercapnia, or by the emergency department or ICU during an acute episode. From January 1997, a prospective protocol of respiratory evaluation was implemented in which all patients were systematically evaluated after the diagnosis of ALS by the Department of Neurology. This protocol consisted of an interview concerning respiratory symptoms (eg, effort dyspnea, orthopnea, sleep disturbances, morning headache, or daytime hypersomnolence) and the following studies: forced spirometry; home nocturnal pulse oximetry; and arterial blood gas levels (measured while the patient was breathing room air). Likewise, on the first visit the patient was informed of the possible respiratory complications and the therapeutic options in an attempt to achieve early decision making. Visits were made every 3 months or on patient demand by telephone contact in the case of the presentation of new respiratory symptoms. The initiation of treatment with NIV was proposed on the occurrence of any of the following situations: the presence of symptoms, especially orthopnea; FVC of ≤ 50% predicted or a decrease in FVC of ≥ 500 mL on two consecutive visits; desaturations in nocturnal pulse oximetry (arterial oxygen saturation, < 90% during 5 consecutive min); or hypercapnia (PaCO₂ > 45 mm Hg).

Comparative Analysis of the Influence of the Protocol

Since 1988, HMV has been proposed as treatment to a total of 86 patients, with all of them accepting a treatment trial. In 22 patients (25%), treatment was not initiated because of intolerance or the inability to adapt to NIV for a minimum of 1 consecutive hour, which was associated in all cases with severe bulbar impairment. Patients rejected tracheostomy and invasive ventilation in this situation. In 15 of the 64 remaining patients (23%), HMV treatment was initiated prior to the implementation of the protocol (group A), and in 49 patients (77%) HMV treatment was initiated after protocol application (group B). The two groups were compared on the initiation of treatment with HMV in terms of general characteristics (eg, demographic variables, respiratory function, gasometry, and pulse oximetry), ventilation access route, and clinical respiratory status. The following four possible clinical conditions were considered: absence of arterial blood gas level alteration (setting 1 [S1]); PaCO₂ of > 45 mm Hg in a stable clinical situation (setting 2); acute respiratory insufficiency (setting 3); or acute respiratory insufficiency requiring ICU admission (setting 4 [S4]). Analysis of survival was performed in patients following treatment with NIV.

Evaluation of the Effects of Bulbar Involvement

In agreement with the Department of Neurology, bulbar involvement was confirmed by the presence of deglutition or phonation alterations. Fifty-four patients (63% of the total population) presented with bulbar involvement on initiating treatment with ventilation. In 32 of these patients (60%), HMV was initiated (NIV, 27 patients), and in 22 patients (40%) NIV was not implemented due to intolerance. To determine the efficacy of NIV and the long-term evolution of these patients, we compared the following: (1) the survival of all patients treated with NIV,
taking into account the presence or absence of bulbar involvement on initiating treatment; and (2) the survival of patients with bulbar involvement who tolerated NIV (treatment group) vs those who were intolerant of NIV (comparison group). Figure 1 contains a diagram of all the patients and the different groups included.

**Statistical Analysis**

Comparison of the groups (group A vs group B, and the treatment group vs the comparison group) was performed using the Student $t$ test for independent samples with numerical variables and the Pearson $\chi^2$ test for comparison of proportions. Analysis of survival was undertaken using the Kaplan-Meier method, applying the log-rank test for between-group comparisons and the Cox regression model for the study of prognostic factors.

### Results

#### Impact of Early Respiratory Evaluation

The results for the 64 patients who initiated therapy with HMV were evaluated. Forty-six patients were male (71%) and 18 patients were female (28%), with a mean age of 60 (SD, 11) years. NIV was initiated with a nasal mask in 57 patients (89%), and in 7 patients (11%) tracheal ventilation was begun during an acute episode (except in 1 patient in whom elective tracheostomy had been carried out prior to the initiation of ventilation).

A greater incidence of tracheal HMV ($p = 0.025$) and initiation of ventilation in an acute setting requiring ICU admission ($S4; p = 0.001$) was observed in group A. However, a lower percentage of patients in whom treatment with HMV was initiated in the absence of respiratory insufficiency ($S1; p = 0.013$), a lower incidence of bulbar involvement ($p = 0.007$), and lesser riluzole treatment ($p = 0.000$) were also observed in this group (Table 1).

Another significant difference observed between the two groups of patients receiving NIV (group A, 11 patients; group B, 46 patients) was a younger age and more severe baseline arterial blood gas abnormalities in patients in group A (Table 2), although no differences were found in the Kaplan-Meier survival curves ($p = 0.23$ [log-rank test]).

#### The Effect of Bulbar Involvement

No significant differences were observed (ie, age, pulmonary function, gasometry findings, nocturnal pulse oximetry findings, and treatment with riluzole) in the group of 57 patients receiving treatment with NIV between the patients presenting with bulbar involvement at the initiation of treatment ($n = 27$) and those without bulbar involvement ($n = 30$), except that the percentage of patients in whom NIV treatment was initiated after the implementation of the protocol of respiratory evaluation was greater in the group with bulbar involvement (96% vs 66%, respectively; $p = 0.004$ [$\chi^2$ test]). The patients without bulbar involvement experienced a significantly greater survival, with a mean of 27 months (SD, 4 months) vs 15 months (SD, 2 months; $p = 0.03$ [log-rank test]) [Fig 2]. With the Cox regression model including possible prognostic factors (ie, age, $P_{CO_2}$, treatment with riluzole, bulbar involvement, and initiation of NIV treatment prior to the protocol), the only independent prognostic factor was bulbar involvement, with a relative risk of 1.6 (95% confidence interval, 1.01 to 2.64; $p = 0.04$).

On the exclusion of patients with bulbar involvement (group B, 96%), the analysis of survival according to the date of NIV treatment initiation showed a significant improvement in survival in patients in group B (mean survival time, 35 months; SD, 6

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**Table 1—Differences Between the Patients in Group A and Group B**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A ($n = 15$)</th>
<th>Group B ($n = 49$)</th>
<th>$p$ Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 initiation</td>
<td>2 (13)</td>
<td>24 (49)</td>
<td>0.013</td>
</tr>
<tr>
<td>S2 initiation</td>
<td>6 (40)</td>
<td>16 (33)</td>
<td>0.92</td>
</tr>
<tr>
<td>S3 initiation</td>
<td>2 (13)</td>
<td>7 (14)</td>
<td>0.60</td>
</tr>
<tr>
<td>S4 initiation</td>
<td>5 (33)</td>
<td>2 (4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tracheal ventilation</td>
<td>4 (26)</td>
<td>3 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bulbar involvement</td>
<td>3 (20)</td>
<td>29 (59)</td>
<td>0.007</td>
</tr>
<tr>
<td>Riluzole treatment</td>
<td>1 (7)</td>
<td>39 (80)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

†Values given as No. of patients (%), unless otherwise indicated. S2 = setting 2; S3 = setting 3.

FIGURE 1. Scheme of the patients and different groups included in the study.
months) compared with group A (mean survival time, 17 months; SD, 4 months; \(p = 0.03\) [log-rank test]), and this improvement persisted on the analysis of global survival after diagnosis (mean survival time, 61 months [SD, 6 months] vs 35 months [SD, 8 months]; \(p = 0.01\) [log-rank test]) [Fig 3].

Last, no significant differences were observed in the characteristics of the patients on the initiation of treatment between the 27 patients with bulbar involvement who tolerated NIV (treatment group) and the 22 patients who did not tolerate NIV (comparison group). A higher mortality rate was found in the survival curves during the first months of follow-up in the group with intolerance to NIV, but the mortality rates later became equivalent, meaning that no significant differences between the two groups were observed for survival time after the initiation of treatment with NIV (\(p = 0.14\) [log-rank test]). On stratification based on \(\text{PCO}_2\) on indication of NIV, no differences were seen in the survival times of patients with normocapnia (treatment group: 11 patients; mean survival time, 14 months [SD, 3 months]; comparison group: 9 subjects; mean survival time, 17 months [SD, 3 months]), while a significant improvement in survival time was observed in the treatment group with \(\text{PCO}_2\) of >45 mm Hg (treatment group: 15 patients; mean survival time, 15 months [SD, 3 months]; comparison group: 13 subjects; mean survival time, 3 months [SD, 1 month]; \(p = 0.0002\) [log-rank test]) [Fig 4].

**Table 2—Differences Between the Characteristics of Group A and Group B on Initiation of NIV**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (n = 11)</th>
<th>Group B (n = 48)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>53 (11)</td>
<td>62 (10)</td>
<td>0.011</td>
</tr>
<tr>
<td>(\text{PaO}_2), mm Hg</td>
<td>66 (16)</td>
<td>75 (14)</td>
<td>0.06</td>
</tr>
<tr>
<td>(\text{PaCO}_2), mm Hg</td>
<td>63 (17)</td>
<td>47 (7) [n = 45]</td>
<td>0.000†</td>
</tr>
<tr>
<td>(\text{SaO}_2), % predicted</td>
<td>50 (19) [n = 6]</td>
<td>52 (17) [n = 34]</td>
<td>0.78†</td>
</tr>
<tr>
<td>(\text{PaO}_2), % predicted</td>
<td>68 (44) [n = 7]</td>
<td>29 (38) [n = 40]</td>
<td>0.01†</td>
</tr>
<tr>
<td>Riluzole treatment, No. of patients</td>
<td>1 (9%)</td>
<td>39 (5%)</td>
<td>0.000†</td>
</tr>
<tr>
<td>PEG, No. of patients</td>
<td>1 (9%)</td>
<td>5 (10%)</td>
<td>0.59†</td>
</tr>
<tr>
<td>Survival time with NIV, mo</td>
<td>16 (13)</td>
<td>17 (16)</td>
<td>0.84†</td>
</tr>
</tbody>
</table>

*Values given as mean (SD), unless otherwise indicated. \(\text{SaO}_2\) = arterial oxygen saturation; PEG = percutaneous endoscopic gastrostomy.
†Determined by \(t\) test.
‡Determined by \(\chi^2\) test.

**Discussion**

Although the role of NIV in the treatment of respiratory complications in ALS patients has been clearly established, few patients are able to benefit from this treatment, and their numbers vary greatly in center-to-center comparisons. In 1999, the American Academy of Neurology published norms\(^{14}\) recommending the initiation of NIV treatment in patients with theoretical FVC values of <50% predicted. However, the reality in American studies is very different. In a survey of 20 centers,\(^{15}\) only 5 centers performed routine patient evaluations by chest physicians, and in a review\(^{16}\) of 2,018 patients,
with an FVC of < 40% predicted received treatment with NIV. The same has been reported in Europe with fewer studies, although in an Italian study\textsuperscript{17} in which 38 centers were surveyed, it was found that in most of the centers the respiratory aspects of the disease were only treated after the first presentation of respiratory symptoms. Thus, in addition to the need to establish criteria for the initiation of ventilation, it is essential to improve the respiratory management of these patients.

In our center, we found that the systematic application of a protocol of early respiratory evaluation improves patient outcomes, particularly in patients without bulbar involvement, in whom survival time increased significantly. This may be attributed to the early application of NIV, since the improvement in survival time was maintained when compared after the diagnosis of the disease. Moreover, although the possibility of an effect of riluzole in group B cannot be discarded, the improvement in survival time was greater than that which would be attributable to the drug\textsuperscript{18} and, in addition, this factor was not significant in the analysis of prognostic factors. Another equally important factor is the improvement in early decision making, since after the application of the protocol the number of patients requiring tracheostomy without prior decision significantly decreased, and no patient chose invasive tracheal ventilation electively after receiving information on the course of the disease following the application of the protocol. On the other hand, NIV can prolong survival even if continuous ventilation is needed.\textsuperscript{19}

Finally, the evaluation of patients after diagnosis with follow-up every 3 months or on patient demand led to the recognition of many patients who were in the initial phases of respiratory insufficiency, thereby enabling the detection of the appearance of respiratory muscular involvement with simple data such as a decrease in FVC repeated on two consecutive visits, the appearance of new symptoms, or minimum desaturations in nocturnal pulse oximetry.

Although it is well-known that the involvement of the oropharyngeal musculature interferes with not only the efficacy but also the tolerance of NIV, few studies have analyzed this in ALS patients who have received treatment with NIV, and these studies have reported contradictory results. While Kleopa et al\textsuperscript{8} did not report differences in the prevalence of bulbar involvement between patients who tolerated and those who did not tolerate NIV (36.8% and 37.5%, respectively), the results of the study by Aboussouan et al\textsuperscript{11} agree with those of our study in observing a significant increase in the number of patients with bulbar involvement in the group with intolerance to NIV (67%). However, in our experience, the percentage of patients who tolerate NIV is greater than that found in these studies. On the one hand, in the absence of bulbar involvement all of the patients tolerated NIV, and only 50% of those presenting with bulbar involvement did not tolerate NIV. Several factors may have influenced these results. The first factor is the positive attitude toward NIV treatment on the part of the multidisciplinary team responsible for the treatment of these patients, which impedes patient refusal to try the treatment. This is in contrast to the 43% of patients who refused to try NIV in the study by Kleopa et al.\textsuperscript{8} The second factor is the wide experience of our group of patients who have received HMV therapy (> 500 patients treated), and the final factor is the establishment of ventilation therapy in the hospital, which probably improves nocturnal adaptation, in contrast to the situation in an outpatient setting.\textsuperscript{11} Cost could be
higher in the hospital setting, but the mean length of stay in our patients was only 4 days, and it should be considered that the frequent outpatient visits that are necessary for the initiation of HMV therapy can be very difficult for ALS patients.

Regarding survival time, the study by Kleopa et al8 also showed results suggesting a trend toward improved survival times with NIV therapy in patients with bulbar involvement vs those without it. These results, however, did not achieve statistical significance and are difficult to explain from a physiopathologic perspective. Similar to the results of the study by Aboussouan et al,11 our results showed a significant improvement in survival time after the initiation of NIV therapy in patients not presenting with bulbar involvement compared to those presenting with it. These differences cannot be attributed to other factors since there were no differences in pharmacologic treatment. One study10 also found the largest benefit of NIV therapy in patients with preserved bulbar function.

The studies by Kleopa et al8 and Aboussouan et al11 agree in their observations of poorer survival times in patients with bulbar involvement who did not tolerate NIV. In both studies, NIV therapy was initiated on the presentation of clear evidence of respiratory musculature involvement (ie, \( P_{CO_2} \geq 45 \) mm Hg and/or orthopnea,11 FVC < 50% predicted, and symptoms8), and their results agree with those of our study with respect to the population initiating NIV with hypercapnia. We did not, however, observe differences in the survival times of patients with bulbar involvement who initiated NIV treatment early compared with those who did not tolerate the treatment. One explanation for the absence of differences in survival times may be the initiation of NIV based on symptoms or alterations secondary to bulbar musculature dysfunction more than respiratory musculature involvement. Nocturnal symptoms such as dyspnea, awakening, choking episodes, or nocturnal desaturations may correspond to deglutitory disorders20 or to obstruction of the upper airway,21 and the specific diagnosis of these alterations may require more complex studies such as polysomnography.22 On the other hand, the suggestion by other authors23 that the lesser the bulbar involvement, the more probable the adaptation to NIV therapy may have influenced the earlier initiation of therapy in this group of patients in whom greater benefits were observed, although our results do not appear to confirm this hypothesis.

In conclusion, it is imperative that a systematic respiratory evaluation should be performed in ALS patients, since this simple strategy improves the indication of NIV therapy with benefits not only in terms of survival time, especially in patients without bulbar involvement, but also with respect to decision making. Our results reinforce those of other studies with regard to improvements in the survival times of patients with bulbar involvement who tolerate NIV when initiated in the setting of respiratory musculature failure, although they do not appear to be confirmed in the early indication of NIV treatment. Prospective and, probably, multicenter studies including a larger number of patients are required to confirm the benefits of early NIV treatment in patients with bulbar involvement and/or the need for a different evaluation protocol to allow the confirmation of the initial alterations of respiratory musculature in these patients.

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