Respiratory Insufficiency with Preserved Diaphragmatic Function in Amyotrophic Lateral Sclerosis

Rika Yamauchi, Tomihiro Imai, Emiko Tsuda, Takayoshi Hozuki, Daisuke Yamamoto and Shun Shimohama

Abstract

Objective We performed a longitudinal study to elucidate the correlation between respiratory insufficiency and respiratory biomarkers, including diaphragmatic compound muscle action potential (DCMAP), at the initiation of noninvasive ventilation (NIV) in patients with amyotrophic lateral sclerosis (ALS).

Methods The patients were assessed at least every six months. Additional assessments were performed at the start of respiratory therapy when the patients met the criteria for the initiation of NIV. Each assessment consisted of a full neurological examination, a phrenic nerve conduction study, respiratory function tests, and nocturnal pulsed oximetry.

Patients We enrolled 43 patients with either definite or probable ALS as defined by the revised El Escorial criteria.

Results The patients were divided into two groups according to the timing of the initiation of respiratory therapy. Seventeen patients (group A) met the criteria for NIV initiation when their DCMAP remained normal. Twenty-six patients (group B) met the criteria when their DCMAP decreased below normal limits. Although respiratory function parameters were significantly worse in group B compared with group A at NIV initiation, more than 80% of the patients in both groups developed nocturnal desaturation during sleep.

Conclusion DCMAP is not always a reliable indicator for determining the optimal timing for NIV initiation during the progression of respiratory insufficiency in ALS. Physicians should be aware of the risk of respiratory insufficiency during sleep in patients with ALS.

Key words: amyotrophic lateral sclerosis, respiratory insufficiency, diaphragmatic compound muscle action potential, sniff nasal inspiratory pressure, nocturnal hypoventilation, noninvasive ventilation


Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects both the upper and lower motor neurons. The involvement of respiratory muscles leads to respiratory dysfunction, which is a major cause of death in ALS (1). Many reports have indicated that noninvasive ventilation (NIV) increases survival and quality of life (QOL) in ALS patients (2-13). Therefore, respiratory function assessment is important for monitoring disease progression and determining the optimal timing for the initiation of NIV.

Pinto and co-workers (14, 15) recently demonstrated that the diaphragmatic compound muscle action potential (DCMAP) predicts hypoventilation in bulbar- and spinal-onset ALS patients. They reported a high negative predictive value and a low positive predictive value of DCMAP, thus implying that an abnormal DCMAP is strongly associated with hypoventilation, but a normal DCMAP does not exclude hypoventilation, and other tests are required. In particular, they recommended using phrenic nerve conduction studies to monitor respiratory function in uncooperative ALS patients (16) who have low motivation, depression, or be-
havioral changes or in bulbar-type ALS with marked facial weakness because weak lip sealing precludes accurate evaluation with conventional respiratory function tests (17). However, there have been few attempts to elucidate the clinical and laboratory characteristics of ALS patients who maintain a normal DCMAP even when developing respiratory insufficiency at the initiation of NIV.

In this study, we conducted a longitudinal study to examine phrenic nerve conduction and other conventional measurements of respiratory function before and at the initiation of NIV. These prospective data reveal the clinical characteristics of respiratory insufficiency with preserved diaphragmatic function in some ALS patients.

**Materials and Methods**

**Subjects and protocol**

Between October 2006 and December 2011, we enrolled 43 patients with definite or probable ALS as defined by the revised El Escorial criteria (18). All patients underwent full neurological, neuroradiological, hematological, and biochemical investigations at entry and throughout the study period until May 2013 or death. The inclusion criteria were that the patient was sufficiently competent to provide informed consent and that regular follow-up confirmed disease progression. Patients with lung disorders, polyneuropathy, cardiac insufficiency, pacemakers, or other debilitating medical conditions were excluded.

Additional assessments were performed when NIV was started in patients who developed respiratory insufficiency and met the criteria for initiation of NIV (see “Criteria for initiation of NIV” below). Each assessment consisted of a full neurological examination, assessment with the ALS functional rating scale-revised (ALSFRS-R) (19), phrenic nerve conduction study, respiratory function tests, and nocturnal pulsed oximetry. The strengths of ten muscles (deltoid, biceps brachii, triceps brachii, wrist extensors, wrist flexors, iliopsoas, quadriceps femoris, hamstrings, tibialis anterior, and gastrocnemius) on both sides were routinely measured by manual muscle testing (MMT). The lowest MMT grades of these upper and lower limb muscles were used in the analyses as the upper and lower limit MMT grades, respectively.

Depending on the timing of NIV initiation, patients were divided into two groups. Group A included patients who met the criteria for initiation of NIV while DCMAP remained within the normal limits. Group B comprised patients who met the NIV criteria with DCMAP below the normal limit.

We also collected DCMAP data from 30 healthy adults (15 men and 15 women) to establish the cutoff values for DCMAP parameters. The control subjects had no neurological or respiratory dysfunction. Their ages ranged from 35 to 70 years (mean age 60), with approximately equal numbers of subjects in each decade (20).

Informed consent was obtained from each subject and the family after the purpose and procedures of the study were explained. The protocol was approved by the local ethics committee.

**Phrenic nerve conduction study**

The subjects’ DCMAPs were recorded using a Viking IV electromyograph (Nicolet Biomedical, Madison, USA). The phrenic nerve was stimulated transcutaneously with 0.2-ms rectangular pulses using a bipolar electrode, and pressure was applied to the cathode inferomedially at the supraclavicular fossa. Each stimulus was timed to occur at the end of an expiration to minimize DCMAP amplitude variation (21-24). Disposable surface disk electrodes (Viking, NEC, Tokyo, Japan) were placed over the xiphoid process (active) and the costal margin in the midclavicular line (reference) in bipolar derivation. The active and reference electrodes were connected to the differential amplitude so that a downward deflection of the waveform represents relative negativity (24). The ground electrode was placed over the upper part of the sternum. Latency was measured as the time to onset of the potential, and amplitude was the height from baseline to the first peak of a DCMAP. The values obtained from the right and left DCMAPs were averaged ([right + left]/2) and used for analysis.

**Respiratory function tests**

The forced vital capacity (FVC) is conventionally used to monitor respiratory function in motor neuron disease, but this method requires the use of a mouthpiece. Sniff nasal inspiratory pressure (SNIP) is a simple and reliable method to measure inspiratory muscle strength; it does not involve the use of a mouthpiece and may be better than FVC or mouth pressures for assessing patients with bulbar signs. Therefore, we performed both tests at each assessment in all patients (25).

The FVC was measured in a sitting position, and the best of three satisfactory expiratory maneuvers, each obtained after a maximal inspiratory effort, was used for the analysis. The SNIP was determined with the patient seated by measuring the pressure through a plug occluding one nostril during sniff performed through the contralateral nostril (MicroRPM, CareFusion, San Diego, USA). The best SNIP measured from the side of the dominant hand was used for the analysis.

**Nocturnal pulsed oximetry and blood gas analysis**

Nocturnal pulsed oximetry was recorded continuously using a finger-tip infrared pulse oxymeter (Pulse Oximetry, Nellcor, Boulder, USA). We recorded mean percutaneous oxygen saturation concentration (SpO2) overnight and the duration of desaturation defined as SpO2 <90%. A nocturnal recording of a minimum of nine hours was used for analysis in this study. A morning blood gas analysis was also performed to measure carbon dioxide partial pressure (pCO2) for each assessment.
Criteria for initiation of NIV

We adopted the following criteria to determine the optimal timing for initiating NIV, in accordance with the guidelines of the Academy of American Neurology (26), the European Federation of Neurological Societies (EFNS) (27), and the Societas Neurologica Japonica (28).

1. Subjective symptoms of intermittent dyspnea, including small voice, shallow breathing, shoulder breathing, feeling of breathing difficulty, excessive fatigue, progressive weight loss, light sleep, and morning headache (29, 30).

2. Nocturnal desaturation defined as SpO2 <90% for at least one cumulative minute during one nocturnal recording (31, 32).

3. A SNIP <50 cmH2O. SNIP correlates well with the transdiaphragmatic pressure and the maximal mouth-inspiratory pressure (MIP). A SNIP of 50 cmH2O is equivalent to an MIP of approximately 60 cmH2O (33-35).

4. Percent FVC <60%. We agree with a previous report that early intervention for respiratory insufficiency can improve both the symptoms and the patients’ QOL (31), although %FVC <50% is the general standard indicator.

5. Hypercapnia as indicated by a pCO2 >45 mmHg in accordance with the above-mentioned guidelines and the standards of many previous reports.

These criteria included subclinical objective laboratory findings of hypoventilation, as well as critical clinical symptoms of respiratory failure. In principle, we initiated NIV when several laboratory criteria were satisfied, even in the absence of any subjective symptoms.

Statistical analysis

The relationships between DCMAP amplitude and other clinical or laboratory parameters were evaluated using Spearman rank correlation coefficient. The patients were divided into two groups according to whether their DCMAP amplitude was preserved (group A) or lowered (group B) when the criteria for NIV were satisfied (see “Patient grouping” below). Differences in baseline characteristics between the two groups were evaluated using the Mann-Whitney U test for continuous variables and Pearson’s chi-squared test for categorical variables. The differences in frequencies of satisfying the five criteria for NIV initiation were analyzed by Pearson’s chi-square test. Disease duration, severity, and respiratory parameters were compared between the two groups with the Mann-Whitney U test. A multiple logistic regression analysis was conducted to identify independent factors associated with grouping. A probability value less than 0.05 was considered statistically significant. The JMP statistical program (SAS Institute Inc., Cary, USA) was used for all data analyses.

Results

Normal DCMAP values

In normal subjects, the latency (mean ± standard deviation [SD]) was 6.8 ± 0.8 ms, and the amplitude was 580 ± 120 μV. These values are similar to those reported for adults by previous investigators (21, 36). In this study, we set 9.2 ms (mean +3 SD) as the cutoff for abnormal latency and 220 μV (mean -3 SD) as the cutoff for abnormal amplitude.

Correlation between DCMAP and other clinical or laboratory parameters

No significant relationship was observed between the DCMAP amplitude and ALSFRS-R bulbar subscore (Spearman correlation coefficient R=-0.14; p=0.38) or total ALSFRS-R score (R=-0.10; p=0.53). On the other hand, DCMAP amplitude correlated significantly with disease duration (R=0.33; p=0.03), SNIP (R=0.47; p=0.004), %FVC (R=0.39; p=0.01), and pCO2 (R=-0.45; p=0.003).

Patient grouping

The patients were divided into two groups according to the timing of NIV initiation. Seventeen patients in group A met the criteria for NIV initiation while DCMAP remained above 220 μV (Figure A). Twenty-six patients in group B met the criteria when DCMAP decreased below 220 μV (Figure B). There were no significant differences between groups A and B regarding the baseline characteristics, including age, sex, onset age, disease duration, bulbar involvement, MMT grades of limb muscles, and pyramidal signs (Table 1).

Group A

NIV was initiated in 16 of 17 patients, due to intermittent dyspnea in eight patients, nocturnal desaturation in 14 patients, SNIP <50 cmH2O in 11 patients, %FVC <60% in six patients, and pCO2 >45 mmHg in four patients. Several patients met multiple criteria simultaneously. The remaining one patient received a tracheostomy instead of NIV according to his own choice when he met four criteria.

Group B

NIV was initiated in 25 of 26 patients due to intermittent dyspnea in 23 patients, nocturnal desaturation in 14 of 22 patients (four patients did not undergo nocturnal recording), SNIP <50 cmH2O in 20 of 23 patients (SNIP could not be measured in three patients), %FVC <60% in 19 patients, and pCO2 >45 mmHg in 21 patients. The remaining one patient received tracheostomy instead of NIV according to his own choice when he met all five criteria.

Status of satisfaction of five criteria

Pearson’s chi-squared tests showed that group B had significantly higher frequencies of intermittent dyspnea (p=
Figure. Representative DCMAP waveforms at baseline (left) and at the initiation of NIV (right) in groups A (upper traces) and B (lower traces). The DCMAP values were within normal limits (>220 μV) at NIV initiation in group A. On the other hand, DCMAP values had decreased significantly at NIV initiation in group B. The bars indicate 10 ms (horizontal) and 200 μV (vertical).

**Table 1. Characteristics of the Patient Groups at Baseline**

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>A (n=17)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>B (n=26)</td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>11/6</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>11/15</td>
<td></td>
</tr>
<tr>
<td>Onset age (yrs)</td>
<td>58.9 ± 12.5</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>63.2 ± 13.0</td>
<td></td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>15.9 ± 7.0</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>16.8 ± 11.4</td>
<td></td>
</tr>
<tr>
<td>Bulbar involvement (%)</td>
<td>58.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Upper limb MMT</td>
<td>3.5 ± 0.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Lower limb MMT</td>
<td>3.8 ± 1.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Hyperreflexia (%)</td>
<td>64.7</td>
<td>0.57</td>
</tr>
<tr>
<td>Babinski sign (%)</td>
<td>82.4</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Group A met the criteria for noninvasive ventilation initiation while diaphragmatic compound muscle action potential (DCMAP) remained above 220 µV. Group B met the criteria when DCMAP decreased below 220 µV. Time and MMT data are expressed as mean ± standard deviation. Upper and lower limb MMTs denote the lowest grades obtained in manual muscle tests on upper and lower limb muscles. Differences between two groups are evaluated using the Mann-Whitney U test for continuous variables and chi-squared test for categorical variables.

**Table 2. Frequencies of Satisfaction of Five Criteria for Initiation of Noninvasive Ventilation by Patients in Groups A and B**

<table>
<thead>
<tr>
<th>Criterion of NIV initiation</th>
<th>Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent dyspnea</td>
<td>A (n=17)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>B (n=26)</td>
<td></td>
</tr>
<tr>
<td>Nocturnal desaturation</td>
<td>82.4%</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>81.8%</td>
<td></td>
</tr>
<tr>
<td>SNIP &lt; 50 cm H2O</td>
<td>64.7%</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>87.0%</td>
<td></td>
</tr>
<tr>
<td>%FVC &lt;60%</td>
<td>35.3%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>73.1%</td>
<td></td>
</tr>
<tr>
<td>pCO2 &gt; 45 mmHg</td>
<td>23.5%</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>80.8%</td>
<td></td>
</tr>
</tbody>
</table>

Group A met the criteria for noninvasive ventilation initiation while diaphragmatic compound muscle action potential (DCMAP) remained above 220 µV. Group B met the criteria when DCMAP decreased below 220 µV. NIV: noninvasive ventilation, SNIP: sniff nasal inspiratory pressure, FVC: forced vital capacity, pCO2: carbon dioxide partial pressure. p values were calculated using Pearson’s chi-squared test.

0.003), %FVC <60% (p=0.01), and hypercapnia as indicated by a pCO2 >45 mmHg (p=0.0002) than group A. On the other hand, there were no significant differences between groups A and B with respect to nocturnal desaturation and SNIP decrease; the frequencies of these two criteria were relatively high in both groups (Table 2).

**Disease duration, ALSFRS-R, and respiratory function parameters**

The disease durations (mean ± SD, months) were 31.4 ± 18.2 in group A and 24.7 ± 11.2 in group B, total ALSFRS-R scores (mean ± SD) were 31.1 ± 5.8 in group A and 32.2 ± 8.1 in group B, and ALSFRS-R bulbar subscores (mean ± SD) were 8.8 ± 2.9 in group A and 9.4 ± 3.2 in group B. These three clinical parameters were not significantly different between groups A and B as assessed with Mann-Whitney U tests (Table 3). However, several respiratory function parameters (mean ± SD) showed significant differences between groups A and B: SNIP (A: 47.4 ± 15.9, B: 31.6 ± 15.6 cmH2O, p=0.01), %FVC (A: 72.1 ± 23.7, B: 53.2 ± 23.5%, p=0.02), pCO2 (A: 42.6 ± 8.4, B: 50.6 ± 8.8 mmHg, p=0.001), and DCMAP (A: 311 ± 69, B: 113 ± 49 µV, p<0.0001) (Table 3). All respiratory function parameters at NIV initiation were significantly worse in group B.
Table 3. Comparison of Disease Duration, Amyotrophic Lateral Sclerosis Functional Rating Scale-revised, and Respiratory Function Parameters between Groups A and B at the Initiation of Noninvasive Ventilation*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=17)</th>
<th>Group B (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (months)</td>
<td>31.4 ± 18.2 (5 - 73)</td>
<td>24.7 ± 11.2 (5 - 45)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total ALSFRS-R score</td>
<td>31.1 ± 5.8 (22 - 43)</td>
<td>32.2 ± 8.1 (17 - 45)</td>
<td>0.53</td>
</tr>
<tr>
<td>ALSFRS-R bulbar subscore</td>
<td>8.8 ± 2.9 (3 - 12)</td>
<td>9.4 ± 3.2 (2 - 12)</td>
<td>0.28</td>
</tr>
<tr>
<td>SNIP (cmH2O)</td>
<td>47.4 ± 15.9 (23 - 74)</td>
<td>31.6 ± 15.6 (10 - 60)</td>
<td>0.01</td>
</tr>
<tr>
<td>%FVC</td>
<td>72.1 ± 23.7 (17.6 - 106.6)</td>
<td>53.2 ± 23.5 (15 - 98.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>42.6 ± 8.4 (28.5 - 68.0)</td>
<td>50.6 ± 8.8 (35.3 - 73.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>DCMAP (µV)</td>
<td>311 ± 69 (220 - 480)</td>
<td>113 ± 49 (0 - 176) &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

All data are expressed as mean ± standard deviation (range). Group A met the criteria for noninvasive ventilation initiation while diaphragmatic compound muscle action potential (DCMAP) remained above 220 µV. Group B met the criteria when DCMAP decreased below 220 µV.

NIV: noninvasive ventilation, ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised.

*Two patients in groups A and B received tracheostomy instead of NIV according to their own choices. Statistical analysis was performed using Mann-Whitney U test.

Table 4. Multivariate Logistic Analysis to Identify Factors Independently Associated with Low Diaphragmatic Compound Muscle Action Potential at Initiation of Noninvasive Ventilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (months)</td>
<td>0.28 (0.002 - 16.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>SNIP (cmH2O)</td>
<td>0.03 (0.000 - 3.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>%FVC</td>
<td>0.66 (0.01 - 40.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>233.3 (3.2 - 89,002.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The parameters that correlated with DCMAP amplitude in Spearman rank correlation analysis were entered in the regression model. SNIP: sniff nasal inspiratory pressure, FVC: forced vital capacity, pCO2: carbon dioxide partial pressure.

Multivariate logistic regression

A multivariate logistic regression analysis was performed to determine the factors independently associated with low DCMAP amplitude at NIV initiation (group B) using disease duration, SNIP, %FVC, and pCO2. Although these four variables were identified as significant parameters associated with DCMAP amplitude by Spearman rank correlation analyses, pCO2 was the only parameter identified by multivariate analysis as independently associated with low DCMAP at NIV initiation (p=0.01) (Table 4).

Discussion

Phrenic nerve stimulation is simple and well tolerated, and it can be performed with surface stimulating and recording electrodes even in infants (24) and the elderly (20). The amplitude of the motor response depends on the number of excitable motor units in the diaphragm (37), but it is also affected by other factors, such as the respiratory cycle (24). To minimize these effects, we stimulated the nerve at the end of the respiratory cycle. This elegant technique can also be applied to ALS patients because it is objective, noninvasive, and highly discriminative for hypventilation during disease progression. Pinto et al. (15) reported that DCMAP detects the loss of motor units in the diaphragm and correlates with other respiratory tests in ALS patients, such as FVC and SNIP, which is consistent with our findings. Furthermore, our present results indicate that the DCMAP amplitude correlates significantly with disease duration, as well as SNIP, %FVC, and pCO2 at NIV initiation. Therefore, phrenic nerve conduction study is useful for the evaluation of respiratory dysfunction in ALS. However, multivariate logistic regression revealed that pCO2 was the only independent factor associated with dividing patients into groups A and B based on low DCMAP amplitude at the initiation of NIV. This means that DCMAP may not be always a significant biomarker to determine the need for NIV. In fact, decreased SNIP and nocturnal desaturation were often observed in patients with respiratory insufficiency but preserved DCMAP, and the frequencies of satisfaction of NIV initiation criteria were not significantly different between groups A and B.

SNIP is known to correlate well with invasive and noninvasive tests of diaphragmatic strength (38) and sternocleidomastoid muscle function (39). Ventilation is not solely dependent on the diaphragm; it requires paraspinal muscles, intercostal muscles, and neck musculature. In patients with preserved DCMAP, a decrease in SNIP may reflect reduced strength in inspiratory muscles other than the diaphragm. Although the influence of repeated measures and the effect of training on SNIP measurement must be noted (40), SNIP should be recommended to monitor respiratory function (15, 35) and predict survival (35) in patients with ALS.

More than 80% of the patients in this study had nocturnal desaturation during sleep irrespective of their DCMAP status. Furthermore, it was obvious that nocturnal hypoventilation did not always coincide with abnormalities in other respiratory function tests conducted during the daytime. These results suggest the need for nocturnal pulsed oximetry to determine when to initiate NIV. Bulbar palsy resulting in
impaired airway clearance may be a major cause of nocturnal desaturation. However, the ALSFRS-R bulbar subscore at NIV initiation did not differ significantly between patients with preserved DCMAP and those with decreased DCMAP. Also, the failure of central respiratory mechanisms leading to reduced responses of the neural systems subserving ventilation to metabolic demand (such as pCO2 level), termed “central drive dysfunction,” may also occur in patients with ALS (41, 42). This may also be another important mechanism of hypoventilation during sleep in ALS.

In conclusion, it is undisputed that some ALS patients will require NIV despite normal respiratory function results. Physicians should therefore be aware of the presence of respiratory insufficiency with preserved DCMAP in patients with ALS. Especially in the setting of nocturnal hypoventilation, the decision to initiate NIV in patients with ALS should be made based on symptoms of sleep disorder and nocturnal pulsed oximetry showing reduced oxygen tension during sleep.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
This study was supported in part by the Program for Developing the Supporting System for Upgrading Education and Research.

References


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