Noninvasive Ventilation Improves Sleep in Amyotrophic Lateral Sclerosis: A Prospective Polysomnographic Study

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Study Objective: To evaluate the effects of noninvasive ventilation (NIV) on sleep in patients with amyotrophic lateral sclerosis (ALS) after meticulous titration with polysomnography (PSG).

Methods: In this prospective observational study, 24 ALS patients were admitted to the sleep laboratory during 4 nights for in-hospital NIV titration with PSG and nocturnal capnography. Questionnaires were used to assess subjective sleep quality and quality of life (QoL). Patients were readmitted after one month.

Results: In the total group, slow wave sleep and REM sleep increased and the arousal-awakening index improved. The group without bulbar involvement (non-bulbar) showed the same improvements, together with an increase in sleep efficiency. Nocturnal oxygen and carbon dioxide levels improved in the total and non-bulbar group. Except for oxygen saturation during REM sleep, no improvement in respiratory function or sleep structure was found in bulbar patients. However, these patients showed less room for improvement.

Conclusions: This study shows an improvement of sleep architecture, carbon dioxide, and nocturnal oxygen saturation at the end of NIV titration and after one month of NIV in ALS patients. More studies are needed to identify the appropriate time to start NIV in bulbar patients. Our results suggest that accurate titration of NIV by PSG improves sleep quality.

Commentary: A commentary on this article appears in this issue on page 511.

Keywords: amyotrophic lateral sclerosis, noninvasive ventilation, sleep architecture, polysomnography


Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder primarily affecting the motor system and is characterized by progressive decrease in muscle strength. In addition to weakness of peripheral muscles, respiratory muscle weakness develops during the course of the disease, leading to reduced alveolar ventilation and respiratory failure, which is the main cause of death in ALS.1,2 A randomized controlled trial showed improvement in survival and quality of life (QoL) in ALS patients treated with noninvasive ventilation (NIV).3 Although survival in the subgroup of patients with severe bulbar impairment did not improve, small improvements in QoL were observed.

Sleep is often disturbed in ALS patients.4–7 In the presence of diaphragmatic dysfunction, REM sleep decreases.8 Furthermore, sleep disturbances and nocturnal desaturations have been observed in ALS patients with normal respiratory function and preserved diaphragmatic innervation.9 Although NIV is predominantly used at night, few studies have examined the effect on sleep in ALS. Nevertheless, NIV could have a negative impact on sleep: wearing a mask and having air blown into the nose and/or mouth do not seem to create the perfect circumstances for good sleep quality. In the presence of weakness of facial or bulbar muscles, application of the mask could create difficulties, resulting in non-intentional leaks. Furthermore, difficulties with swallowing and managing secretions could interfere with NIV during sleep.10 Conversely, improvement of oxygensation and carbon dioxide levels would have beneficial effects on sleep. Most studies dealing with sleep in ALS are based on patient-reported outcomes and reported improved sleep after NIV initiation.11–14 Only two

BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous research has shown an improvement in survival and quality of life after initiation of NIV in ALS. Until now, no improvement in objective sleep parameters has been found; however, NIV was titrated during daytime. More detailed titration with polysomnography could perhaps improve quality of sleep.

Study Impact: This study shows that NIV titration with polysomnography improves objective sleep outcomes in ALS patients. Hence, meticulous titration of NIV has an important clinical impact in this patient group. Further research is necessary to create evidence to find the correct time to start NIV in bulbar ALS patients.
studies used polysomnography (PSG) to evaluate sleep during NIV and did not demonstrate improvement in sleep. Katzberg et al. showed an improved oxygenation but no improvement in sleep efficiency (SE), sleep arousals and sleep architecture during NIV. Atkeson et al. showed a high frequency of patient-ventilator asynchronies (PVA). Therefore, additional studies evaluating the effect of NIV on sleep are needed.

The aim of this prospective study was to evaluate the influence of NIV on sleep in ALS by PSG with capnography before and after one month of NIV. Correlations were searched between therapeutic compliance with carbon dioxide measurement, improvement in patient-reported outcomes (total scores), and improvement in objective sleep parameters. Although a previous study shows no improvement in sleep structure, we hypothesized that improvement in sleep structure could be found with a more meticulous NIV titration.

METHODS

Patients
At University Hospitals Leuven, ALS patients are routinely followed at the Neuromuscular Reference Centre (NMRC) in collaboration with pulmonologists (BB, DT). Patients with decreased inspiratory muscle strength (maximal inspiratory mouth pressure [MIP] < 60 cm H2O), restrictive pulmonary function (vital capacity [VC] < 80% of the predicted value) and at least one of the following criteria were offered NIV: symptoms of nocturnal alveolar hypoventilation, increased daytime arterial carbon dioxide ([P_ACO2] > 45 mm Hg) or an increase ≥ 10 mm Hg in transcutaneous carbon dioxide (PtcCO2) during sleep compared to their awake supine value (≥ 40 mm Hg). These inclusion criteria ensured that all patients in this study fulfilled the NIV criteria according to the guidelines of the American Academy of Neurology and the guidelines of the American Academy of Sleep Medicine (AASM) by 2 physicians with large experience in PSG analysis. During diagnostic PSG, airflow was detected by a thermistor (Braebon, NY, USA) and nasal pressure cannula system (Teleflex Medical, NC, USA). A pneumotachograph (Hamilton Medical, Bonaduz, Switzerland) was used to record flow during NIV titration. Apnea and hypopnea were scored according to the AASM 2012 guidelines. PtcCO2 was continuously monitored by a Tosca 500 monitor (Radiometer Ltd., Brønshoj, Denmark). The PtcCO2 and pneumotachograph data were incorporated in the PSG software and continuously followed.

Before and after 1 month of NIV, patients performed a VC measurement in sitting and (if possible) supine position according to the guidelines of the European Respiratory Society, with prediction equations as proposed by Quanjer. Daytime arterial blood gas (ABG) analysis was carried out in sitting position without ventilatory support. Measurements of MIP and sniff nasal inspiratory pressure (SNIP) were performed (MicroRPM, Micro Medical, Brooklyn, NY, USA). Patients completed questionnaires concerning sleep, QoL, and functionality. The Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) were used to measure sleep quality and daytime sleepiness, respectively. Apart from the short-form 36 health questionnaire (SF-36), a generic measurement searching for health-related QoL, we employed the McGill Quality of Life questionnaire (MQoL) measuring QoL specifically in patients with a life-threatening disease. Functionality was measured by the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). Bulbar function was based on the first 3 questions of the ALSFRS-R, and patients were classified as bulbar when this score was ≤ 9.

This study was registered at clinicaltrials.gov (NCT01889043) and approved by the local ethical committee (ML7674). Written informed consent was obtained from all participants.

Statistical Analysis
Statistical analyses were performed with SAS 9.0 (SAS Institute Inc., Cary, NC, USA). Data are reported as mean ± standard deviation or as median and interquartile range. Comparisons between pre and post measurements were performed by paired t-test or Wilcoxon signed-rank test, depending whether data were normally distributed or not. Between-group comparisons were performed by unpaired t-test or Mann-Whitney test. Spearman rho and Pearson were used to test correlations. Results were considered significant when p < 0.05. Figures were made by GraphPad Prism 5.01 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

From January 2012 to April 2013, 63 patients were referred to our unit by the NMRC. Twenty-four patients (60 ± 10 years, 21 males) were started on NIV (Figure 1). Demographic data and baseline measurements of inspiratory muscle strength, VC, and ABG are shown in Table 1. Measurement of supine VC could not be performed in 7 patients because of severe orthopnea. Three patients refused ABG analysis, and 2 patients had problems performing MIP/SNIP measurement. The most prevalent symptoms of alveolar hypoventilation were orthopnea (20 patients), increased daytime sleepiness (17 patients),
NIV Improves Sleep in ALS

Frequent awakenings (15 patients), and exertional dyspnea (12 patients). In our group, 10 patients showed important bulbar involvement and were classified as “bulbar”; 14 patients were classified as “non-bulbar.” Seventeen patients were discharged from the hospital on spontaneous/timed (S/T) mode and 7 patients on S mode, due to intolerance of S/T mode (5 of these patients had bulbar involvement with residual saliva and swallowing problems which aggravated with the S/T mode and thereby influencing their subjective and objective sleep quality). Nineteen patients were ventilated by nasal mask and 5 patients by oronasal mask. IPAP was set at 14 ± 2 cm H₂O and EPAP was set at 4 ± 1 cm H₂O. Patients on S/T mode had a back-up frequency of 16 ± 2/min. One non-bulbar male patient died of pneumonia before follow-up, and one bulbar male patient could not be tested with NIV after one month because of intolerance (1.8 h/day use, only during daytime). These 2 patients were excluded from further analysis.

After one month (38 ± 9 days), ALSFRS-R was significantly decreased (p < 0.01 for all patients; p < 0.05 for non-bulbar patients or bulbar patients). Daytime P_a CO₂ decreased significantly in the total group (46 ± 6 vs. 43 ± 5 mm Hg, p < 0.05) and non-bulbar patients (48 ± 6 vs. 43 ± 5 mm Hg, p < 0.05).

### Sleep Architecture

At baseline, PSG revealed poor sleep quality (Table 2). A low SE, with low percentages of slow wave sleep (N3) and REM sleep, and an increased arousal-awakening index (AAI) were present. Sleep quality of bulbar patients was better than sleep quality of non-bulbar patients, with less stage 1 sleep (N1), more REM sleep, and a lower AAI. Except for one patient who had no N3, all sleep stages were present in bulbar patients, while N3 and REM sleep were absent in 8 and 5 non-bulbar patients, respectively.

After one month, several changes in sleep architecture were present. AAI and percentage of N1 sleep were significantly reduced and percentages of N3 and REM sleep were significantly increased (while total sleep time was not significantly higher) in all patients. The same observations were made in the group of non-bulbar patients, with even a significant increase in SE. In the non-bulbar group all sleep stages were now present in all patients but one. In the bulbar patients, no improvement in SE, sleep stages, or AAI was found (Table 2).

Analyzing PSG of the night with the final settings during the start-up procedure already found improvements in sleep structure compared to diagnostic PSG. The total group showed improvement in AAI (17 [12–21] per hour of sleep; p < 0.01) and the amount of N1 (4 [2–9] %; p < 0.01), N3 (19 [8–30] %; p < 0.01) and REM (21 [14–26] %; p < 0.05) sleep, while the non-bulbar group showed improvement in SE (81 [67–84] %; p < 0.01), AAI (18 [13–22] per hour of sleep; p < 0.01), and N1 (3 [2–9] %; p < 0.01), N3 (19 [4–30] %; p < 0.05), and REM (25 [20–29] %; p < 0.01) sleep. Bulbar patients showed no improvement at discharge.

### Sleep Respiratory Parameters

At diagnostic PSG, patients showed few obstructive events (0.0 [0.0–0.3] obstructive apneas per hour of sleep; 0.1 [0.0–6.3] obstructive hypopneas per hour of sleep). Table 3 shows improvements in SpO₂% and P_a CO₂. In the total group the time spent with SpO₂% < 90% improved during the total night as well as in REM and N1 and stage 2 (N2) sleep. Time spent with P_a CO₂ > 55 mm Hg improved during the total night measurement, N1, N2, and N3 sleep. Non-bulbar patients showed significant changes in the same parameters as the total group. Additionally, a trend to improvement was found for time spent with SpO₂% < 90% in N3 (p = 0.0579). Bulbar patients only

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**Figure 1**—Flow chart of patient inclusion.

- 63 patients were referred by the NMRC
- 24 patients did not meet the criteria to start NIV
- 6 patients who were acutely started NIV at the intermediate intensive care unit
- 6 patients refused NIV
- 27 patients were admitted to the LUCS
- 3 patients were intolerant after mask application and refused further NIV use
- 24 patients were started NIV
- 1 patient died before follow-up
- 1 patient did not tolerate NIV at home
- 22 patients were analysed

NMRC, neuromuscular reference centre; NIV, noninvasive ventilation; LUCS, Leuven University Centre For Sleep/Wake Disorders.

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**Table 1**—Demographic data and baseline measurements of arterial blood gases, vital capacity, and inspiratory muscle strength.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 24)</th>
<th>Non-bulbar (n = 14)</th>
<th>Bulbar (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>21/3</td>
<td>13/1</td>
<td>8/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 10</td>
<td>61 ± 8</td>
<td>58 ± 13</td>
</tr>
<tr>
<td>Time from ALS symptom onset (months)</td>
<td>26 ± 13</td>
<td>27 ± 14</td>
<td>25 ± 12</td>
</tr>
<tr>
<td>Daytime P_a CO₂ (mm Hg)</td>
<td>46 ± 6</td>
<td>48 ± 6</td>
<td>42 ± 3*</td>
</tr>
<tr>
<td>Daytime P_a O₂ (mm Hg)</td>
<td>77 ± 12</td>
<td>72 ± 12</td>
<td>86 ± 7*</td>
</tr>
<tr>
<td>VCSAT (%pred)</td>
<td>56 ± 14</td>
<td>60 ± 16</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>VCSUP (%pred)</td>
<td>41 ± 9</td>
<td>43 ± 11</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>MIP (cm H₂O)</td>
<td>−35 ± 12</td>
<td>−38 ± 11</td>
<td>−30 ± 13</td>
</tr>
<tr>
<td>SNIP (cm H₂O)</td>
<td>−25 ± 21</td>
<td>−22 ± 26</td>
<td>−30 ± 11</td>
</tr>
</tbody>
</table>

Data are given as mean ± standard deviation. *p < 0.05 bulbar vs. non-bulbar. P_a CO₂, partial pressure of carbon dioxide in arterial blood; P_a O₂, partial pressure of oxygen in arterial blood; VCSAT, seated vital capacity; VCSUP, supine vital capacity; MIP, maximal inspiratory pressure; SNIP, sniff nasal inspiratory pressure.
improved in time spent with SpO₂ % < 90 % in REM sleep. In the bulbar group, no changes were found in P tc CO₂ measurement.

Analyzing the data of SpO₂ % and P tc CO₂ of the night with the final settings during titration showed improvements in comparison with the diagnostic PSG. The total group improved in the time spent with SpO₂ % < 90 % during the total night (4 [0–49] %; p < 0.01), N1+N2 (3 [0–48] %; p < 0.01), and REM (1 [0–50] %; p < 0.01) sleep, and also in time spent with SpO₂ % < 90 % during the total night (4 [0–49] %; p < 0.01), N1+N2 (3 [0–48] %; p < 0.01), and REM (1 [0–50] %; p < 0.01) sleep, while bulbar patients only reported an improved PSQI total score (9.0 [6.5–12.5] vs 5.0 [4.0–9.0]; p < 0.01) and sleep duration (1.0 [0.0–2.0] vs 0.0 [0.0–0.5]; p < 0.01). Improvements were found in the SF-36 emotional health subscale for the total (50 [25–77] vs 65 [54–98]; p < 0.0001), non-bulbar (50 [25–84] vs 68 [54–90]; p < 0.01), and bulbar group (50 [25–67] vs 60 [56–77]; p < 0.01). Vitality changed only for the total (35 [10–50] vs 50 [29–60]; p < 0.05) and non-bulbar groups (25 [10–49] vs 48 [26–60]; p < 0.01).

**Compliance**

Therapeutic compliance was significantly correlated with initial daytime P tc CO₂ (Figure 2A). Furthermore, NIV use was correlated with baseline nocturnal P aCO₂ and changes in P tc CO₂ measurements over 1 month (Table 5). Figure 2B shows a statistical significant relationship between compliance and change in MQoL total score in the total group and non-bulbar group. No correlation was found between therapeutic compliance and any objective sleep parameter.

**DISCUSSION**

This is the first study demonstrating improvements in sleep architecture and respiratory parameters in ALS patients during treatment with nocturnal NIV, measured by PSG. The total

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### Table 2—Sleep structure in all, non-bulbar and bulbar patients before and after one month of NIV use.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 22)</th>
<th>Non-bulbar (n = 13)</th>
<th>Bulbar (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>TST (min)</td>
<td>317 (216–442)</td>
<td>351 (261–455)</td>
<td>311 (107–428)</td>
</tr>
<tr>
<td>SE (%)</td>
<td>59 (40–72)</td>
<td>68 (50–80)</td>
<td>62 (19–81)</td>
</tr>
<tr>
<td>N1 (%)</td>
<td>11 (6–32)</td>
<td>8 (4–14)*</td>
<td>10 (0–6)</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>63 (37–75)</td>
<td>54 (46–63)</td>
<td>63 (36–77)</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>1 (0–10)</td>
<td>15 (8–19)*</td>
<td>0 (0–6)</td>
</tr>
<tr>
<td>REM (%)</td>
<td>9 (1–16)</td>
<td>18 (9–23)*</td>
<td>10 (0–12)</td>
</tr>
<tr>
<td>AAI (n/h)</td>
<td>37 (16–55)</td>
<td>17 (11–21)**</td>
<td>42 (36–82)</td>
</tr>
</tbody>
</table>

*p < 0.05 pre vs. post. **p < 0.01 pre vs. post. *p < 0.05 bulbar vs. non-bulbar. #p < 0.05 bulbar vs. non-bulbar. TST, total sleep time; SE, sleep efficiency; N1, stage 1 sleep; N2, stage 2 sleep; N3, slow wave sleep; REM, rapid eye movement sleep; AAI, arousal-awakening index; pre, before NIV; post, after 1 month of NIV.

### Table 3—Measurements of oxygen saturation and transcutaneous carbon dioxide measurements at baseline and after one month of NIV treatment.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 22)</th>
<th>Non-bulbar (n = 13)</th>
<th>Bulbar (n = 9)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>PtcCO₂ N1+N2 &gt; 55 (%)</td>
<td>50.3 (0.0–98.1)</td>
<td>0.0 (0.0–2.3)**</td>
<td>89.4 (0.0–98.9)</td>
</tr>
<tr>
<td>PtcCO₂ REM &gt; 55 (%)</td>
<td>42.5 (0.1–95.4)</td>
<td>0.0 (0.0–5.7)**</td>
<td>78.7 (5.2–95.9)</td>
</tr>
<tr>
<td>PtcCO₂ total night &gt; 55 (%)</td>
<td>40.4 (1.4–97.9)</td>
<td>0.0 (0.0–6.2)**</td>
<td>48.0 (2.3–99.1)</td>
</tr>
<tr>
<td>PtcCO₂ N3 &gt; 55 (%)</td>
<td>55.8 (0.0–100.0)</td>
<td>0.0 (0.0–0.0)*</td>
<td>100.0 (75.0–100.0)</td>
</tr>
<tr>
<td>PtcCO₂ REM &gt; 55 (%)</td>
<td>35.3 (2.1–100.0)</td>
<td>0.5 (0.0–3.0)*</td>
<td>37.1 (12.6–100.0)</td>
</tr>
<tr>
<td>PtcCO₂ N3 &lt; 90 (%)</td>
<td>8.3 (0.0–72.0)</td>
<td>0.0 (0.0–0.1)</td>
<td>57.3 (4.3–100.0)</td>
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<tr>
<td>PtcCO₂ total night &gt; 55 (%)</td>
<td>10.4 (1.4–97.9)</td>
<td>0.0 (0.0–6.2)**</td>
<td>48.0 (2.3–99.1)</td>
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</table>

Data are given as median (25th–75th percentile). *p < 0.05 pre vs. post. **p < 0.01 pre vs. post. #p < 0.05 bulbar vs. non-bulbar. SpO₂, oxygen saturation; PtcCO₂, transcutaneous carbon dioxide; REM, rapid eye movement sleep; N3, slow wave sleep; N1+N2, stage 1 and 2 sleep; Pre, before NIV; post, after 1 month of NIV.
Table 4—Measurements of Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality index (PSQI), and McGill quality of life questionnaire (McGill) at baseline and after one month.

<table>
<thead>
<tr>
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<th>All (n = 22)</th>
<th>Non-bulbar (n = 13)</th>
<th>Bulbar (n = 9)</th>
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<td>ESS</td>
<td>8.0 (3.8–10.0)</td>
<td>4.5 (3.0–7.3)*</td>
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<tr>
<td>PSQI_tol</td>
<td>8.5 (6.8–13.3)</td>
<td>5.0 (3.0–8.3)**</td>
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<tr>
<td>PSQI_tol</td>
<td>1.5 (1.0–2.0)</td>
<td>1.0 (0.0–1.0)**</td>
<td>2.0 (1–2.5)</td>
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<td>PSQI_tol</td>
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<td>0.5 (0.0–1.3)</td>
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<td>PSQI_tol</td>
<td>1.0 (0.0–2.0)</td>
<td>0.0 (0.0–0.0)**</td>
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<td>PSQI_tol</td>
<td>2.0 (0.0–3.0)</td>
<td>0.0 (0.0–1.0)**</td>
<td>2.0 (0.0–3.0)</td>
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<td>PSQI_lat</td>
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<td>0.0 (1.0–1.0)**</td>
<td>1.0 (1.0–2.0)</td>
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<td>PSQI_nad</td>
<td>0.0 (0.0–3.0)</td>
<td>0.0 (0.0–2.3)</td>
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<tr>
<td>PSQI_dat</td>
<td>2.0 (1.0–2.0)</td>
<td>1.0 (1.0–2.0)</td>
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<tr>
<td>MQL_sgr</td>
<td>5.0 (3.0–7.0)</td>
<td>7.0 (4.8–7.0)</td>
<td>5.0 (2.5–7.0)</td>
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<tr>
<td>MQL_int</td>
<td>5.1 (4.1–6.3)</td>
<td>6.3 (5.0–7.5)**</td>
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<tr>
<td>MQL_phys</td>
<td>3.3 (1.8–5.4)</td>
<td>5.0 (3.7–7.5)*</td>
<td>2.7 (1.7–4.5)</td>
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<tr>
<td>MQL_phys</td>
<td>4.0 (3.0–5.3)</td>
<td>5.0 (3.8–7.0)*</td>
<td>3.0 (3.0–4.5)</td>
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<tr>
<td>MQL_yssyn</td>
<td>4.9 (2.5–7.0)</td>
<td>7.0 (5.3–8.5)*</td>
<td>3.8 (2.3–6.8)</td>
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<td>MQL_sed</td>
<td>5.8 (4.2–6.8)</td>
<td>6.3 (4.6–7.6)</td>
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<tr>
<td>MQL_sup</td>
<td>8.3 (6.8–10.0)</td>
<td>8.0 (6.9–9.5)</td>
<td>9.0 (7.3–10.0)</td>
</tr>
</tbody>
</table>

Data are given as median (25th–75th percentile). *p < 0.05 pre vs. post. **p < 0.01 pre vs. post. #p < 0.05 bulbar vs. non-bulbar. ESS, Epworth Sleepiness Scale; PSQI_tol, Pittsburgh Sleep Quality index total score; PSQI_int, sleep quality; PSQI_lat, sleep latency; PSQI_dur, sleep duration; PSQI_eff, sleep efficiency; PSQI_dist, sleep disturbances; PSQI_nad, sleep medication; PSQI_dat, sleep dysfunction; MQL_sgr, McGill Quality of Life questionnaire single item scale; MQL_tot, total score; MQL_phys, physical symptoms; MQL_phys, physical well-being; MQL_yssyn, psychological symptoms; MQL_sed, existential well-being; MQL_sup, support; Pre, before NIV; Post, after one month of NIV.

Figure 2—Correlation between therapeutic compliance and daytime arterial carbon dioxide before NIV and change in quality of life.

(A) Correlation between daytime arterial carbon dioxide (n = 19) before NIV initiation and use hours: r = 0.54, p < 0.05. (B) Correlation between change in the total score of the McGill questionnaire (ΔMQoLtot) and use hours in the total group (r = 0.56, p < 0.01) and non-bulbar group (gray dots) (r = 0.63, p < 0.05). PaCO2, partial pressure of carbon dioxide in arterial blood; ΔMQoLtot, change in the total score of the McGill Quality of Life questionnaire.

In our study, NIV improved (apart from gas exchange) PSG-recorded and patient-reported sleep and QoL. Few studies showed improvement in sleep by patient-reported outcomes in ALS. Lyall et al. did not make a distinction between bulbar and non-bulbar patients, but VC in their patients was similar to our group. Without specifying time of follow-up, they found a significant improvement in ESS score. Butz et al. showed a long-term improvement of sleep quality by using the PSQI, also without distinction between bulbar and non-bulbar...
the PSQI score and its subscale of sleep duration. In Katzberg’s study, NIV was titrated during daytime according to the patient’s comfort. In our study, the Trilogy 100 was used with the AutoTrak setting. Katzberg et al. did not mention their trigger modality, but fixed trigger sensitivity could influence the number of PVA and AAI, as trigger sensitivity could possibly differ between sleep stages. Another difference is the use of average volume-assured pressure support (AVAPS) in Katzberg’s study. Until now, no randomized controlled trial with AVAPS has been performed in ALS. Impact of self-changing pressures on leaks, PVA, and sleep is therefore unknown. Although in a heterogenic group of neuromuscular patients, volume-targeted ventilation has shown to cause more PVA than pressure support ventilation. Katzberg et al. already suggested that an additional night of PSG to titrate NIV would have been helpful to optimize treatment in their cohort. In stable neuromuscular patients, with at least 3 months of NIV use, 66% still showed a PSQI score ≥ 5 (mean score 6.98 ± 3.2). In that study, NIV was established following evaluation of diurnal comfort, respiratory function, and gas exchange, and of nocturnal in-hospital cardiopulmonary polygraphic monitoring, but without any account the increased functional disability. Another limitation is the limitation of our data to results after one month. Butz et al. showed that patient-reported improvements in sleep emerge after one month of NIV treatment and could last for up to 10 months. As the goal of NIV is improving sleep and QoL and

### Table 5—Correlations of therapeutic compliance (use hours) with baseline measurements of time of transcutaneous carbon dioxide spent > 55 mm Hg and changes over one month in time of transcutaneous carbon dioxide spent > 55 mm Hg.

<table>
<thead>
<tr>
<th>Use Hours</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{TCO_2} &gt; 55$ total night</td>
<td>0.68</td>
<td>0.0009</td>
</tr>
<tr>
<td>$P_{TCO_2} &gt; 55$ REM</td>
<td>0.62</td>
<td>0.0084</td>
</tr>
<tr>
<td>$P_{TCO_2} &gt; 55$ N3</td>
<td>0.70</td>
<td>0.0073</td>
</tr>
<tr>
<td>$P_{TCO_2} &gt; 55$ N1+N2</td>
<td>0.70</td>
<td>0.0007</td>
</tr>
<tr>
<td>$\Delta P_{TCO_2} &gt; 55$ REM</td>
<td>0.53</td>
<td>0.0365</td>
</tr>
<tr>
<td>$\Delta P_{TCO_2} &gt; 55$ N3</td>
<td>0.73</td>
<td>0.0076</td>
</tr>
<tr>
<td>$\Delta P_{TCO_2} &gt; 55$ N1+N2</td>
<td>0.61</td>
<td>0.0041</td>
</tr>
</tbody>
</table>

$\Delta$, change over 1 month; $P_{TCO_2}$, transcutaneous carbon dioxide; REM, rapid eye movement sleep; N3, slow wave sleep; N1+N2, stage 1 and 2 sleep
NIV Improves Sleep in ALS

simultaneously increasing survival, longitudinal studies on the effect of NIV on sleep and the effect of improved sleep quality on survival are definitely needed. We know that PSG is not routinely used during NIV titration in most countries. Probably, three nights of titration with PSG (as performed in this study) will not be necessary in most patients; however, the findings of this study underline the importance of PSG during NIV titration in patients with ALS.

CONCLUSIONS

This is the first prospective study showing objective improvement in different sleep parameters after one month of NIV in ALS. Increased amounts of N3 and REM sleep with a decreased AAI and improved gas exchange were observed, especially in patients with none or mild bulbar involvement. Furthermore, patients reported better sleep and QoL. In patients with severe bulbar involvement, almost no improvement was found, and additional research is needed on when NIV should be started in these patients. This study suggests that meticulous titration of NIV by PSG could improve sleep in patients with ALS.

ABBREVIATIONS

AAI, arousal-awakening index
ABG, arterial blood gas
ALS, amyotrophic lateral sclerosis
EPAP, expiratory positive airway pressure
MIP, maximal inspiratory mouth pressure
MQuol, McGill Quality of Life questionnaire
NIV, non-invasive ventilation
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
PVA, patient-ventilator asynchronies
QoL, quality of life
REM, rapid eye movement
SAQLI, Sleep Apnea Quality of Life Index
SE, sleep efficiency
SNIP, sniff nasal inspiratory pressure
VC, vital capacity

REFERENCES


ACKNOWLEDGMENTS

The authors thank the team members of the Neuromuscular Reference Centre Leuven (University Hospitals Leuven, Belgium) and the Leuven University Centre for Sleep/Wake Disorders (University Hospitals Leuven, Belgium) for their assistance in data collection. Bart Vrijsen thanks the Clinical Research Foundation, UZ Leuven, Belgium and ABMM-Telethon for their financial support.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2014
Submitted in final revised form January, 2015
Accepted for publication January, 2015
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.