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Diaphragm pacing improves sleep in patients with amyotrophic lateral sclerosis

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Abstract

In amyotrophic lateral sclerosis (ALS) patients, respiratory insufficiency is a major burden. Diaphragm conditioning by electrical stimulation could interfere with lung function decline by promoting the development of type 1 muscle fibres. We describe an ancillary study to a prospective, non-randomized trial (NCT00420719) assessing the effects of diaphragm pacing on forced vital capacity (FVC). Sleep-related disturbances being early clues to diaphragmatic dysfunction, we postulated that they would provide a sensitive marker. Intramuscular diaphragm pacers were implanted laparoscopically in 18 ALS patients for daily conditioning. ALS functioning score (ALSFRS), FVC, sniff nasal inspiratory pressure (SNIP), and polysomnographic recordings (PSG, performed with the stimulator turned off) were assessed before implantation and after four months of conditioning ($n = 14$). Sleep efficiency improved ($69 \pm 15\%$ to $75 \pm 11\%$, $p = 0.0394$) with fewer arousals and micro-arousals. This occurred against a background of deterioration as ALSFRS-R, FVC, and SNIP declined. There was, however, no change in NIV status or the ALSFRS respiratory subscore, and the FVC decline was mostly due to impaired expiration. Supporting a better diaphragm function, apnoeas and hypopnoeas during REM sleep decreased. In conclusion, in these severe patients not expected to experience spontaneous improvements, diaphragm conditioning improved sleep and there were hints at diaphragm function changes.

Key words: Amyotrophic lateral sclerosis, respiratory insufficiency, diaphragm, diaphragm pacing, sleep-related disturbances

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of unknown origin leading to death one to three years after diagnosis (1–4). Motor neuron cell death leads to progressive weakness of muscles. Respiratory muscle weakness and the corresponding respiratory failure are prominent negative prognostic factors in ALS. It is associated with reductions in quality of life and survival (1,3,5–6), respiratory failure being the most common cause of death in ALS patients (7). Specifically, the involvement of the diaphragm in the degenerative process is associated with dyspnoea (8), sleep alterations (9),

and reduced life expectancy (9). Riluzole, a blocker of tetrodotoxin-sensitive sodium channels, can delay the onset of ventilator dependence and prolong survival by a few months (10), but there is no curative treatment for ALS. Non-invasive ventilation (NIV) is now part of the standard of care for patients with advanced respiratory insufficiency (11–13). NIV alleviates dyspnoea, improves sleep, and prolongs life.

In the absence of curative therapy, symptomatic approaches aimed at improving muscle strength and/or endurance could be considered. Moderate improvements of unknown clinical relevance have

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[AQ1]

1 been observed in response to inspiratory muscle
2 training (14) and the administration of theophyl-
3 lines that slightly increase respiratory muscle
4 endurance (15).

5 Electrical neuromuscular stimulation of striated
6 muscles can improve their function (16), and
7 preliminary observations have suggested that low
8 frequency electrical stimulation of limb muscles
9 could be beneficial in Duchenne's myopathy (17)
10 and in ALS (18). Regarding the diaphragm, dia-
11 phragm pacing can reverse diaphragm disuse
12 atrophy in quadriplegic patients (19,20). It is also
13 known, from animal models, to promote the devel-
14 opment of oxidative fatigue-resistant type 1 muscle
15 fibres (21–23). It has therefore been hypothesized
16 that low frequency electrical stimulation of the dia-
17 phragm could slow the decline in vital capacity (or
18 forced vital capacity) that is characteristic of ALS.
19 It could also be that ALS-related phrenic degenera-
20 tion is heterogeneous (24), and that there can be a
21 variable distribution of upper and lower motor
22 neuron losses. Exploratory attempts at electrically
23 conditioning the diaphragm in ALS patients through
24 intra-diaphragmatic phrenic nerve stimulation
25 have shown sufficient promise for a multicentre
26 trial to be launched with the approval of the US
27 Food and Drug Administration (ClinicalTrials.gov
28 NCT00420719). This trial was designed to deter-
29 mine the effect of diaphragm pacing on a primary
30 endpoint of forced vital capacity decline. As of
31 March 2011, the results of this trial are pending and
32 will be the subject of a separate report.

33 The present article reports on an ancillary
34 study to NCT00420719 performed within the
35 cohort of patients implanted at the French partici-
36 pating centre. In this study, the impact of diaphragm
37 pacing on sleep has been assessed using polysomno-
38 graphic recording.

39 There is a close link between diaphragm function
40 and sleep abnormalities, both in general (review
41 in 25,26) and during ALS where diaphragm weak-
42 ness is associated with REM sleep-related episodes
43 of hypoventilation and deteriorated sleep architec-
44 ture and efficiency (9,27). Respiratory related
45 sleep disturbances can be observed in patients
46 with diaphragmatic dysfunction who otherwise
47 exhibit little spirometric abnormality (26,28). This
48 suggests that they are sensitive markers (although of
49 unknown specificity). It was therefore hypothesized
50 that, irrespective of results on forced vital capacity,
51 a positive effect of diaphragm pacing on diaphragm
52 function could improve sleep efficiency and other
53 sleep characteristics in ALS patients.

54 **Methods**

55 *Trial design and participants*

56 The study reported here was ancillary to a prospec-
57 tive, non-randomized, multicentre, interventional

61 trial of a laparoscopically implanted diaphragm
62 pacing device (NeuRx Diaphragm Pacing System
63 (DPS)TM, Synapse, Oberlin, Ohio, USA) in 106
64 patients with ALS, conducted at seven North
65 American centres and one French centre (Clinical-
66 Trials.gov NCT00420719). This trial was designed
67 to assess the impact of the DPS on the decline of
68 forced vital capacity (FVC).

69 The sleep study described here involved patients
70 attending the French centre. Local ethics committee
71 approval was obtained. The patients gave written
72 consent in accordance with the Declaration of
73 Helsinki. Eligibility criteria were as for the main
74 study, namely that patients had to be aged 18 years
75 or older, with familial or sporadic ALS diagnosed as
76 laboratory-supported probable, probable or definite
77 according to the World Federation of Neurology
78 El Escorial criteria; with bilateral hemidiaphragm
79 mobility documented fluoroscopically during a
80 sniff test; an FVC between 50% and 85% of pre-
81 dicted values at screening (and greater than 45% of
82 predicted at time of implant) and no underlying
83 cardiac or respiratory diseases likely to increase risk
84 from general anaesthesia. Negative pregnancy test-
85 ing in females of childbearing potential was required.
86 Patients were excluded if they had gross cognitive
87 dysfunction likely to impair their ability to function
88 with the device.

89 *Procedures for implantation and* 90 *operation of the device*

91 The surgical technique for device implantation is
92 described elsewhere (29,30). Briefly, following
93 mapping to identify optimal diaphragm stimulation
94 sites (31), two electrodes were implanted laparo-
95 scopically in each hemidiaphragm. Electrode leads
96 were tunnelled to a percutaneous exit site. A subcu-
97 taneous fifth electrode served as an anode. All
98 leads were connected to the external stimulator.
99 Diaphragm contractions were induced 8–18 times
100 per min by delivering trains of stimuli (15 Hz fre-
101 quency, pulse width 90–150 μ s, intensity 8–18 mA
102 as tolerated). The patients were instructed to use the
103 DPS device for three to five 30-min stimulation ses-
104 sions per day, and were allowed to use it more if they
105 so wished. They were asked to fill in daily logs of
106 their stimulation sessions. In addition, they were
107 provided with a set of six 500-h batteries and
108 instructed to ask for replacements when the fourth
109 battery had run out. This provided a rough method
110 to verify their actual use of the device.

111 *Data collection*

112 After inclusion (M0), there was a three-month
113 lead-in period. The primary data collection was
114 made at the end of the third month (M3), immedi-
115 ately before implantation. Repeat assessments were
116 performed at months 5, 7, 9, and 12 (i.e. 2, 4, 6 and
117 120

9 months post-implant). Collected data comprised ALS functional rating scale (ALSFRS-R); quality of life assessment (SF-36 questionnaire); spirometric variables including forced vital capacity (FVC) (32); respiratory muscle variables including sniff nasal inspiratory pressure (SNIP) (33), maximal inspiratory and expiratory pressures ($P_{i,max}$ and $P_{e,max}$, respectively) (34); blood gases; fluoroscopic diaphragm evaluation; tolerance and safety information.

In the patients in the ancillary sleep study additional measurements at M3 and after four months of diaphragm stimulation (M7) were performed. These included diaphragm function testing (oesophageal, gastric and transdiaphragmatic pressure twitch response – $P_{es,tw}$, $P_{ga,tw}$ and $P_{di,tw}$, to supramaximal bilateral anterior magnetic stimulation (BAMPS) (35), according to recommended procedures (36). Sleep assessments included the Epworth score and full-night laboratory polysomnographic recordings (PSG). These recordings included three electroencephalograms (Fp1/Cz, O2/Cz, C3/A2), bilateral electrooculogram, surface electromyogram of the chin, leg muscles, and inspiratory neck muscle, airflow via nasal pressure transducers (during unassisted breathing) or a pneumotachograph (during non-invasive ventilation), tracheal sounds through a microphone, thoracic and abdominal belts, electrocardiogram, and finger pulse oximetry.

These recordings were performed while the patients were breathing spontaneously or under non-invasive ventilation depending on their current clinical status, but always with the stimulator off.

The sleep stages (37), arousals (38), and respiratory events (39) were scored visually according to international criteria. Hypopnoea was defined as more than 50% decrease in airflow associated with a 3% oxygen desaturation or an arousal. Outcomes

of particular interest were total sleep time, sleep efficiency, sleep latency, duration of stage N1-N2, N3 and REM sleep, arousal index, apnoea and hypopnoea index during sleep and during REM sleep, the proportion of time spent with an SpO_2 (transcutaneous pulsed oxygen saturation) below 90% and inspiratory neck muscle use expressed as the ratio of the time spent with a visible EMG activity to total sleep period. The study design is summarized in Figure 1.

Statistical analysis

To minimize bias, the analysis was not restricted to those of the implanted patients who underwent both the M3 and the M7 sleep studies ('sleep studies' cohort, $n=14$), but it was conducted on the whole 'implanted cohort' ($n=18$). Missing data were categorized as non-informative (not relating to the outcome under study) or informative (missing systematically or possibly relating to the outcome, e.g. where a patient was physically unable to perform a test). Statistical comparisons were conducted after imputing non-informative missing data with the median of the observed data from the sleep studies cohort, and imputing informative missing data with the 10th or 90th percentile, whichever coincided with the worst performance relative to the median. Data were summarized using the mean, standard deviation, median, minimum and maximum for continuous variables and number and percent for categorical variables. Continuous variables were paired within patients and statistical significance (defined as a probability p of a type 1 error below 0.05) was assessed using the Wilcoxon signed rank test. Of importance, the imputing process had minimal effects on the significance levels when

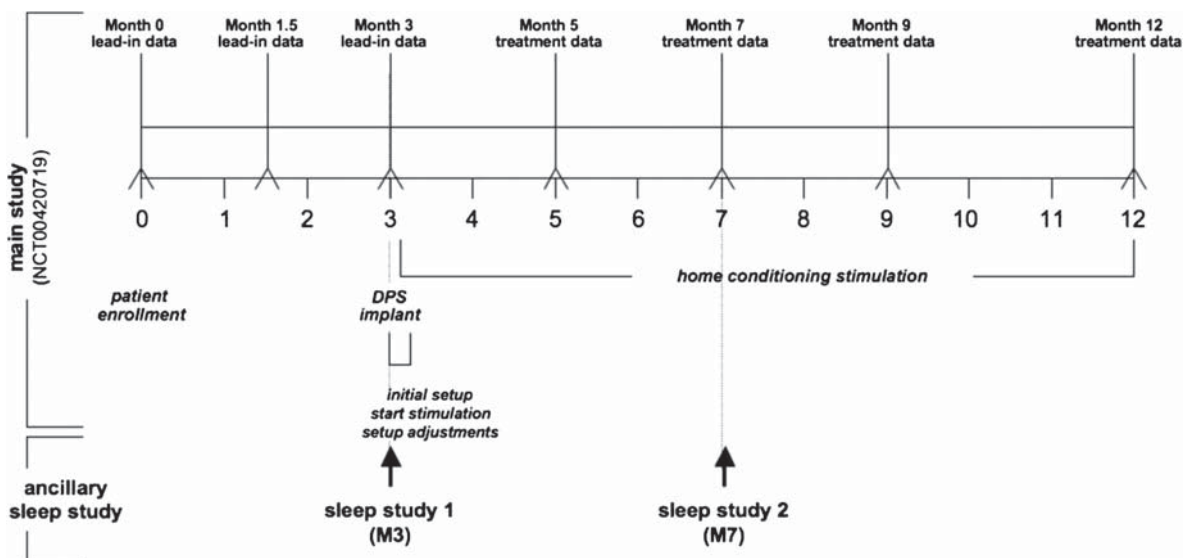


Figure 1. Study design showing timing of the additional measures performed in the patients included at the French centre of the multicentre trial ('sleep study'). These included full night polysomnography and the assessment of the diaphragm response to bilateral phrenic nerve stimulation (twitch pressures).

1 comparing the analysis of observed versus imputed
2 data (results not shown). Given the exploratory
3 nature of the study, the interpretation of the results
4 was conducted from the uncorrected analysis, but a
5 multiplicity correction was performed for informa-
6 tion using Hochberg's procedure (40).

8 Results

9
10 Thirty-eight patients were screened between
11 September 2008 and March 2009. Twenty-four met
12 the inclusion criteria and were enrolled. Among
13 these, one died from massive inhalation during the
14 run-in period, one withdrew consent, and four had
15 an excessive fall in FVC (FVC less than 45% at the
16 end of the run-in). As a result, 18 patients were
17 implanted (Figure 2). There were no serious adverse
18 events during or following anaesthesia or relating to
19 device insertion. Mean hospital stay was two days.
20 Minor complaints of shoulder pain on initiation of
21 stimulation were resolved by adjustment to stimula-
22 tor settings (final settings at seven months: pulse
23 width $116.6 \pm 30.4 \mu\text{s}$, intensity $9.65 \pm 3.35 \text{ mA}$).
24 The 18 implanted patients ('implanted cohort')
25 completed baseline sleep studies and diaphragm
26 stimulation derived measurement at M3. Fourteen
27 of them completed evaluations at four months after
28 device implantation (M7) ('sleep studies' cohort)
29 (Table I). Of these 14 patients, six were classified
30 clinically as having a predominantly 'upper motor
31 neuron' form, six a predominantly 'lower motor
32 neuron' form, and two a 'balanced' form.

33 The stimulation logs showed that all the patients
34 in the sleep studies cohort used their stimulator
35 according to the instructions received (eight patients
36 were very consistent in performing five sessions each

61 day; three started with three sessions and increased
62 to five after two months; and three started with three
63 sessions, went to five, and then stimulated them-
64 selves for several hours per day). The number of
65 missed days between M3 and M7 never exceeded
66 eight except in two cases (55 and 60 days). In addi-
67 tion, 11 patients in the sleep cohort continued to
68 order batteries after M7, which indicates a sustained
69 use of the device after the end of the sleep study.

70 The ALSFRS-R deteriorated between M3
71 and M7 (Table II), without significant change in its
72 respiratory subscore. No significant change was
73 observed in the SF-36 score.

74 FVC declined significantly (Table II). This decline
75 (from $66 \pm 12\%$ predicted to $58 \pm 18\%$) was princi-
76 pally expiratory in nature. The expiratory reserve
77 volume (ERV) declined from $70 + 32\%$ predicted
78 to $54 + 27\%$ ($p = 0.0134$), while the decline in
79 inspiratory capacity (IC) did not reach statistical
80 significance. The $P_{i,\text{max}}$ and $P_{e,\text{max}}$ declined at
81 similar rates of magnitude, but only the decline
82 in $P_{e,\text{max}}$ was statistically significant (Table II).
83 Twitch pressures were low to start with ($P_{\text{es,tw}}$
84 $7.3 \pm 5.9 \text{ cm H}_2\text{O}$, for an expected value above
85 11 (36); $P_{\text{di,tw}}$ $9.3 + 7.2 \text{ cm H}_2\text{O}$, for an expected
86 value above 20 (36)). They deteriorated significantly
87 during the follow-up period (Table II).

88 Between M3 and M7, none of the patients
89 was put on any form of sedative treatment. Half of
90 the patients were already on NIV at the time of
91 implantation (Table I). In this subpopulation there
92 was no settings change between the two sleep
93 studies. The other half of the patients was not under
94 NIV at the time of implantation, and in this sub-
95 population there was no case of NIV initiation
96 between the two sleep studies.

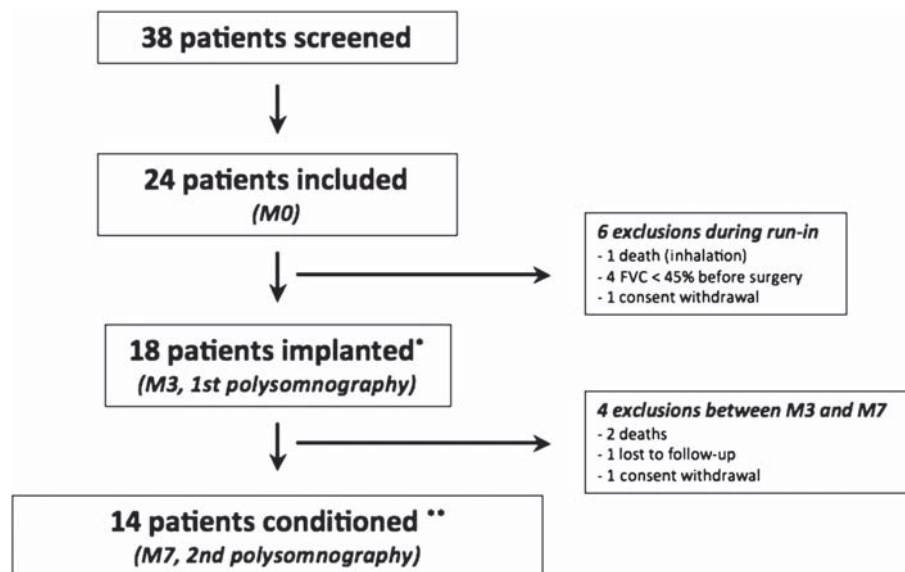


Figure 2. Flow chart of the French ancillary sleep study.

*50% of the patients received non-invasive ventilation (NIV) at the time of implantation (M3).

**There was no change in NIV status or NIV duration during the four-month diaphragm conditioning period, i.e. between M3 and M7.

Table I. Demographics and disease characteristics of patients, as observed at inclusion (M0).

	Observed $n = 18$ Implanted cohort	Observed $n = 14$ Sleep study cohort
Gender		
Male	10 (56%)	9 (64%)
Female	8 (44%)	5 (36%)
Age at inclusion (years)	66 ± 6 (66) 52 – 76	66 ± 6 (67) 52 – 76
Weight (kg)	65 ± 10 (63) 50 – 85	64 ± 10 (62) 50 – 85
Height (m)	1.7 ± 0.1 (1.7) 1.6 – 1.8	1.7 ± 0.1 (1.7) 1.6 – 1.7
BMI (kg/m ²)	23.6 ± 3.1 (24.1) 18.5 – 28.5	23.1 ± 3.3 (22.5) 18.5 – 28.5
Disease duration at inclusion (months)	42 ± 27 (35) 9 – 124	43 ± 30 (33) 9 – 124
ALSFRS-R at inclusion	34.0 ± 7.8 (36.0) 15 – 42	33.0 ± 8.2 (36.0) 15 – 42
Site of disease onset		
Bulbar	2 (11%)	2 (14%)
Limb	16 (89%)	12 (86%)
Bulbar involvement*	9.9 ± 2.4 (10.5) 4 – 12	9.7 ± 2.6 (10.5) 4 – 12
Use of riluzole	17/18 (94%)	13/14 (93%)
Use of NIV at inclusion	9/18 (50%)	7/14 (50%)
Use of PEG at inclusion	0/18 (0%)	0/14 (0%)
FVC (% predicted), sitting	69 ± 10 (68) 54 – 92	71 ± 9 (69) 54 – 92
IC (% predicted), sitting	69 ± 18 (73) 40 – 98 N = 15	71 ± 16 (74) 45 – 98 N = 12
ERV (% predicted), sitting	78 ± 28 (74) 46 – 131 N = 15	77 ± 28 (75) 46 – 131 N = 12
SNIP (% predicted)	42 ± 24 (36) 16 – 108	45 ± 26 (42) 16 – 108
Pi,max (% predicted)	57 ± 28 (54) 16 – 128 N = 17	59 ± 30 (57) 16 – 128 N = 13
Pe,max (% predicted)	40 ± 18 (36) 18 – 66 N = 15	42 ± 18 (36) 21 – 66 N = 11
pH	7.42 ± 0.02 (7.42) 7.39 – 7.45	7.42 ± 0.02 (7.42) 7.39 – 7.45
PaO ₂ (mmHg)	77 ± 12 (80) 39 – 88	80 ± 7 (80) 70 – 88
PaCO ₂ (mmHg)	46 ± 8 (44) 35 – 73	44 ± 3 (44) 35 – 49
Inclusion-implantation delay (months)	3.2 ± 0.2 (3.2) 2.8 – 3.9	3.2 ± 0.3 (3.2) 2.8 – 3.9

*Bulbar involvement = sum of ALSFRS-R speech, salivation and swallowing scores.
Values as mean ± SD (median) (min-max) $n =$ (if less than value supplied in column header).

BMI: body mass index; ALSFRS-R: amyotrophic lateral sclerosis functional rating scale; NIV: non-invasive ventilation; PEG: percutaneous endoscopic gastrostomy; FVC: forced vital capacity volume; IC: inspiratory capacity; ERV: expiratory reserve; SNIP, sniff nasal inspiratory pressure; Pi,max: maximal static inspiratory pressure measured at the mouth; Pe,max: maximal static expiratory pressure measured at the mouth (predicted values from Black and Hyatt).

pH, PaO₂, PaCO₂ from arterial samples taken during unassisted spontaneous room air breathing.

ERV and IC are the expiratory and inspiratory components of VC, respectively.

Regarding sleep, we did not observe significant changes in the Epworth sleepiness scale, in gross sleep architecture, and in the percentage of time spent with an SpO₂ below 90% (Table III). Time in stages N1, N2, N3 and REM sleep remained similar over the study period. Sleep efficiency significantly improved from 69 + 15% to 75 + 11% ($p = 0.0394$) (Table III, Figure 3a). This was driven by a decrease in the time spent awake after sleep onset (wake after sleep onset, WASO), from a mean of 182 min to 136 min ($p = 0.0032$) (Table III, Figure 3b). The arousal index (awakenings and micro-awakenings, the latter not accounted for in the WASO) was also significantly reduced from a mean of 22 per h to 16 per h ($p = 0.0005$) (Table III, Figure 3c). While the overall apnoea-hypopnoea index was unchanged (Table III), there was a significant reduction in the REM-related apnoea-hypopnoea index from a mean of 10.4 per h to 4 per h ($p = 0.045$) (Table III). The use of neck muscle during sleep, as studied from EMG recordings (see Methods), decreased significantly between M3 and M7 ($p = 0.0093$). Only two patients in the sleep studies cohort clearly deteriorated in terms of the above sleep characteristics, in spite of reporting using the stimulator. The others were either stable ($n = 2$) or improving ($n = 10$).

There was no discernible relationship between DPS application and the studied outcomes (including in the two patients who deteriorated). There were also no obvious differences between bulbar and spinal onset patients, and no obvious differences between upper motor neuron versus lower motor neuron patients (although the two patients who deteriorated had a dominant pattern of lower motor neuron lesions).

Discussion

This study shows that after four months of diaphragm conditioning, patients with ALS exhibit significant sleep improvements, irrespective of their status regarding NIV. Sleep efficiency increased (median 9%), with a reduction in arousal index driving a decrease of wake after sleep onset (median 69 min). These changes are all the more noteworthy that they occurred against a background of continuing deterioration (of the ALSFRS-R score, of FVC, of respiratory pressures). They were therefore observed in patients not expected to experience any form of spontaneous improvement. Of note, no comparable NIV data are available. As an indication of the magnitude of the observed effect, we note that widely prescribed pharmacological treatments for primary insomnia increase sleep efficiency by 6–7% and reduce wake after sleep onset by 15–20 min (41,42). The risks associated with surgical implantation of the stimulators were low, as already reported (29).

Sleep studies can be confounded by the so-called ‘first-night effect’ where patients, unfamiliar with

Table II. ALSFRS-R and respiratory variables at month 3 (M3; baseline) and month 7 (M7; four months after device implantation and diaphragm conditioning). (Implanted cohort) (Difference imputed).

Parameter	Observed and imputed			
	Observed		Difference (M7 - M3) n = 18	p-value#
	M3	M7		
ALSFRS-R	30 ± 7 (30) 14 - 42 n = 18	25 ± 8 (24) 12 - 34 n = 15	-4.9 ± 6.1 (-1.0) -18 - 2	0.0032*
VC (% predicted)	66 ± 12 (64) 49 - 89 n = 18	58 ± 18 (63) 22 - 85 n = 15	-9.4 ± 10.8 (-8.5) -29 - 19	0.0024*
ERV (% predicted)	70 ± 32 (65) 26 - 136 n = 18	54 ± 27 (49) 21 - 117 n = 15	-14.1 ± 21.4 (-11.5) -37 - 39	0.0134*
IC (% predicted)	65 ± 22 (58) 27 - 115 n = 18	58 ± 21 (59) 22 - 89 n = 15	-10.3 ± 21.2 (-5.8) -62 - 24	0.0817
SNIP (% predicted)	37 ± 16 (32) 19 - 70 n = 15	33 ± 19 (24) 8 - 70 n = 15	-9.1 ± 8.6 (-8.0) -21 - 15	0.0010*
Pi,max (% predicted)	47 ± 19 (45) 20 - 85 n = 16	44 ± 18 (44) 12 - 77 n = 15	-6.1 ± 16.8 (0) -35 - 18	0.3510
Pe,max (% predicted)	32 ± 18 (29) 10 - 73 n = 14	28 ± 17 (27) 7 - 59 n = 15	-6.3 ± 7.6 (-6.5) -18 - 15	0.0027*
Pes, twitch with BAMPS(cmH ₂ O)	7.3 ± 5.9 (4.8) 1.1 - 19.0 n = 17	5.3 ± 5.4 (3.5) 0 - 16.4 n = 15	-2.5 ± 3.5 (-1.8) -13.1 - 3.7	0.0055*
Pga, twitch with BAMPS (cm H ₂ O)	3.1 ± 2.6 (2.8) 0 - 8.3 n = 14	2.6 ± 3.1 (2.0) -2.3 - 9.0 n = 15	-1.4 ± 2.0 (-0.9) -6.5 - 1.3	0.0160*
Pdi, twitch with BAMPS (cm H ₂ O)	9.3 ± 7.2 (6.3) 1.9 - 24.6 n = 14	7.5 ± 8.0 (4.8) 0 - 25.4 n = 15	-3.6 ± 4.9 (-2.5) -19.7 - 3.7	0.0009*

#Wilcoxon signed rank test.

*Remained statistically significant after application of the Hochberg multiple testing procedure.

Values as mean ± SD (median) (min-max) n = (if less than value supplied in column header).

FVC: forced vital capacity; ERV: expiratory reserve volume; IC: inspiratory capacity;

SNIP: sniff nasal inspiratory pressure; Pi,max: maximal static inspiratory pressure measured at the mouth; Pe,max: maximal static expiratory pressure measured at the mouth; Pes: oesophageal pressure; BAMPS: bilateral anterior magnetic stimulation; Pga: gastric pressure; Pdi: transdiaphragmatic pressure, computed as Pga-Pes.

the sleep laboratory environment, experience a deterioration of their sleep during their first night in the laboratory (43). In our patients, the comparison of the M3 and M7 nights (Table III) did not show any of the characteristics of the first-night effect (namely, more N1-N2, less N3, less REM, a longer sleep latency) (43). In addition, six patients had undergone a sleep recording for clinical reasons prior to their inclusion in the study. There was no significant difference between these prior nights and the M3 nights (time lag five to eight months) regarding the first-night effect criteria (Table IV). A placebo effect cannot be excluded (a reason why it was decided against including a sleep quality questionnaire among the outcomes). However, the pattern of sleep improvement and its pathophysiological coherence go against the likelihood of a placebo effect being the sole explanation of the results. Other concerns could be raised. The study population was

small, but significant changes were observed in key indices of sleep. Most of them, if not all, resisted the correction for multiplicity. Not all patients completed the second sleep study at M7, but this was accounted for conservatively at imputation. There was no control group because this study was ancillary to a larger one that was powered on FVC and during which the patients served as their own controls. It is therefore not possible to determine with certainty whether, or how, the evolution of ALS was influenced by the intervention. In spite of these limitations that are real and of importance, the observed sleep improvements were physiologically coherent and, again, occurred in spite of a general and respiratory decline. For these reasons, we believe that these results are important and require close consideration.

Although they are fragmentary, there are arguments to support the hypothesis that diaphragm

Table III. Sleep and neck muscle use data M3–M7 ($n = 18$ Cohort (Difference imputed)).

Variable	Observed		Observed and imputed	
	M3 ($n = 18$)	M7 ($n = 14$)	Difference (M7–M3) ($n = 18$)	p -value [#]
Epworth sleepiness score (0–24)	5.9 ± 4.0 (5.5) 1.0 – 13.0	6.0 ± 5.1 (5.0) 0 – 20.0	–0.8 ± 3.1 (–2.0) –6.0 – 8.0	0.0745
Total sleep period (min)	582 ± 60 (566) 484 – 710	551 ± 118 (551) 304 – 758	–42 ± 107 (–19) –246 – 140	0.0969
Total sleep time (min)	370 ± 119 (404) 1.2 – 521	411 ± 112 (413) 212 – 557	26 ± 104 (35) –111 – 256	0.6013
Sleep efficiency (%)	69 ± 15 (70) 33 – 90	75 ± 11 (76) 51 – 88	8 ± 12 (9) –13 – 28	0.0394*
Sleep latency (min)	35 ± 41 (23) 0 – 179	53 ± 51 (33) 10 – 153	11 ± 52 (5) –127 – 109	0.3829
Stage N1–N2 (% of total sleep time)	63 ± 12 (65) 40 – 85	67 ± 14 (66) 41 – 93	0.1 ± 12.1 (0.9) –16.6 – 20.3	0.9229
Stage N3 (% of total sleep time)	20 ± 10 (19) 3 – 41	20 ± 12 (17) 1 – 38	1.3 ± 10.3 (4.6) –13.0 – 23.7	0.9068
REM (% of total sleep time)	16 ± 5 (16) 8 – 25	14 ± 7 (15) 0 – 24	–1.4 ± 6.9 (–0.5) –13.0 – 12.6	0.4748
Wake after sleep onset (min)	182 ± 102 (173) 54 – 474	136 ± 65 (114) 63 – 264	–59 ± 73 (–69) –210 – 73	0.0032*
Arousal Index (per h)	22 ± 10 (22) 6 – 42	16 ± 8 (14) 9 – 38	–6 ± 7 (–7) –21 – 6	0.0005*
Apnoea-hypopnoea index (per h)	8 ± 15 (1) 0 – 56	5 ± 9 (1) 0 – 32	–4 ± 10 (–1) –35 – 4	0.1196
REM Apnoea-hypopnoea index (per h)	10.4 ± 19.0 (1.4) 0.0 – 58.7	4.0 ± 7.0 (0.0) 0.0 – 24.5	–7.4 ± 15.8 (–1.8) –58.7 – 6.8	0.0450
Neck muscle use (% of total sleep period)	34 ± 28 (22) 5 – 100 $n = 14$	27 ± 25 (17) 5 – 100	–5.2 ± 9.3 (–3.8) –29.6 – 12.4	0.0093
Time spent with SpO ₂ less than 90% (% of total sleep period)	2.6 ± 4.6 (0.2) 0.0 – 16.6	4.1 ± 7.0 (1.2) 0.0 – 21.5	1.4 ± 4.3 (0.0) –7.9 – 10.8	0.2661

[#]Wilcoxon signed rank test.

*Remained statistically significant after application of the Hochberg multiple testing procedure.

Values as mean ± SD (median) (min–max), with mention of n = if less than supplied in column header.

REM: rapid eye movements sleep; SpO₂: transcutaneous pulsed oxygen saturation.

pacing was efficient in interfering with diaphragm function, as follows. FVC decreased in our patients, but to interpret this finding properly it must be kept in mind that the FVC manoeuvre consists of a maximal inspiration (inspiratory capacity) and a maximal expiration (expiratory reserve volume) performed sequentially. A reduction in FVC can therefore result from an inspiratory ailment, an expiratory one, or both. In our patients, the reduction in FVC was driven by a reduction in the expiratory component (Table II), on which diaphragm conditioning would not be expected to have any direct effect. In contrast, there was no significant decrease in inspiratory capacity (Table II). This is compatible with diaphragm pacing altering the course of diaphragmatic degeneration against a background of expiratory deterioration. Similarly, maximal expiratory pressure decreased but that was not the case with maximal inspiratory pressure (Table II). Another and perhaps stronger argument in favour of an actual effect of diaphragm conditioning is the reduction in REM sleep-related hypopnoea (Table III) that occurred between M3 and M7. REM sleep constitutes

the most vulnerable period in the presence of respiratory muscle weakness, and REM sleep related episodes of hypoventilation are closely linked with diaphragmatic dysfunction (9,25,26). Furthermore, our patients exhibited a significant decrease in inspiratory neck muscle activity at night. However, patients suffering from diaphragm paralysis have an increased recruitment of extradiaphragmatic inspiratory muscle at night (28), and there is a link between diaphragmatic dysfunction and inspiratory neck muscle use in ALS patients (8,44). It is thus reasonable to speculate that the reduced neck muscle activity in our patients was possible because of an improved diaphragm function. It is important to note that improvements in sleep were seen in patients who received NIV at M3 as well as in patients who did not. This further supports the argument that diaphragm pacing did indeed change diaphragm function.

One intriguing question at this stage is how to reconcile an improvement in diaphragm function allowing sleep to improve with the observed reductions in sniff nasal inspiratory pressure and twitch

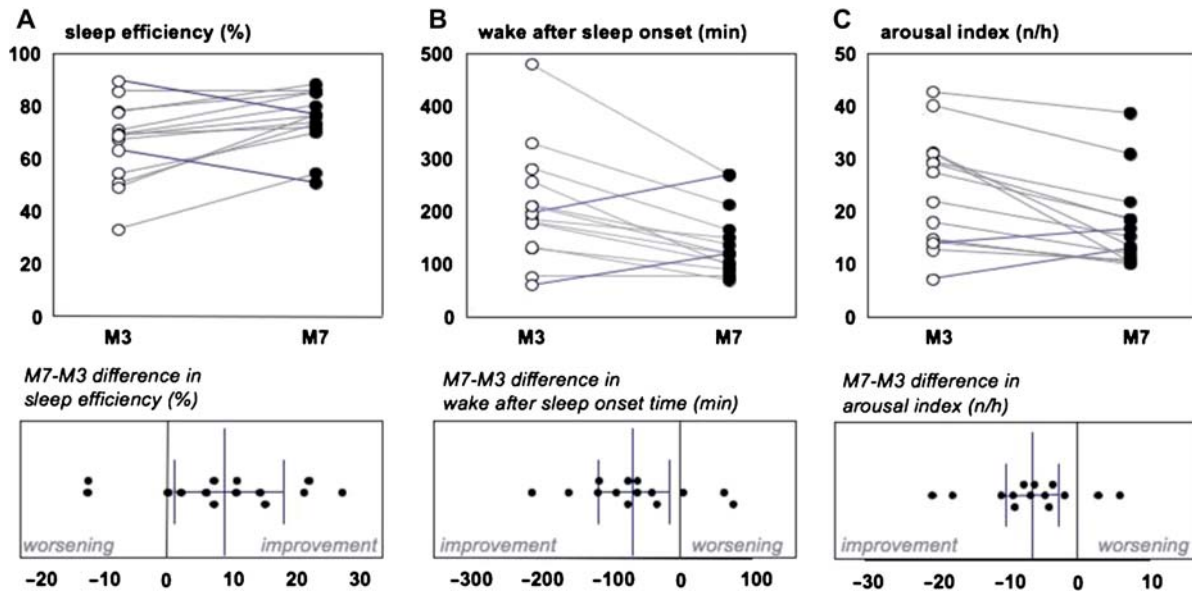


Figure 3. Sleep efficiency (A), wake after sleep onset (B) and arousal index (C) depicted as individual patients' 'before-after' plots (top row; M3: white squares. M7: black circles) and as the M7-M3 difference (bottom row; individual values with the median and interquartile space).

pressures. Chronic, low-frequency, electrical stimulation of a muscle can change its fibre type composition (45,46). In the diaphragm, for example, animal models have shown that the 'normal' mixture of rapid and slow fibres is replaced after a few weeks by a uniform population of slow fibres (21–23). Experience from diaphragm pacing in quadriplegic patients suggests that this also occurs in humans, the increase in contractility during diaphragm reconditioning being accompanied by a progressive reduction in the stimulus frequency at which fusion of the contraction is observed (47). Slow fibres are important for muscle endurance but they produce less force than fast fibres. Thus, an improved diaphragm endurance despite a loss of diaphragm strength is theoretically possible. Similar phenomena have been observed in response to electrical conditioning of striated muscles (48,49). This would explain positive effects of diaphragm conditioning on ventilation during REM sleep-improved endurance – that would be concomitant with reductions in twitch pressures and SNIP (loss in force) – that are more dependent on fast fibres. In this perspective, SNIP – fast contraction – decreased in our patients while static inspiratory pressure – slow contraction – did not significantly do so. To further test the 'endurance hypothesis' and strengthen the evidence regarding the putative effect of pacing on diaphragm properties, we conducted a post-hoc analysis of the sniff nasal inspiratory pressure (SNIP) tracings obtained in the 'sleep cohort' patients. During the SNIP procedure, the patients perform several (ca. 10) sniff manoeuvres in succession. We hypothesized that 1) because our patients already had markedly weak muscles at the time of inclusion, this could

suffice to induce fatigue-compatible changes in the SNIP dynamics; 2) a positive effect of diaphragm pacing on diaphragmatic endurance would reduce the magnitude of such changes. We observed that at M3, the SNIP value corresponding to the last effort performed during a given 'sniff session' was significantly lower than the SNIP value produced during whichever of the first three efforts was the best (12% on average, $p = 0.0085$, Wilcoxon signed rank test). This is compatible with incipient fatigue, whatever its origin. In contrast, at M7, this difference was not present (+1% on average, n.s.) even though the SNIP value had declined. Future studies should specifically address this issue in a prospective manner.

In conclusion, we submit that the sleep improvements observed in our patients give this study a reasonably strong proof-of-concept value. The findings are all the more important given that these patients would have been expected to deteriorate over the duration of the protocol. The study therefore provides a rationale for future work aimed at delineating the clinical relevance of diaphragm conditioning in ALS, and at defining optimal target populations (pacing should be more beneficial in patients with predominant upper motor neuron forms), implantation timing, and stimulation parameters.

To answer these questions, randomized controlled trials will be needed both to corroborate our findings and to determine how diaphragm conditioning and NIV will interact and complement one another. Meanwhile, it should be kept in mind that in a condition that has such a poor prognosis, every step that has the potential to alleviate symptoms and improve quality of life represents a significant advance.

Table IV. First-night effect criteria.

Parameter	Pre-study (n = 6)	M3 (n = 14)	Difference (M3-PreStudy) (n = 6)	p-value [#]
Total sleep time	442 ± 94 (471) 282 – 532 n = 5	378 ± 75 (404) 236 – 464	-23.4 ± 51.9 (-11.0) -90 – 45 n = 5	0.3125
Sleep latency	32 ± 18 (23) 19 – 63 n = 5	38 ± 45 (23) 10 – 179	2.6 ± 17.8 (-2.0) -19 – 29 n = 5	1.000
Stage 1-2 duration	63 ± 10 (64) 46 – 72 n = 5	66 ± 12 (67) 41 – 85	8.4 ± 14.7 (8.0) -10.4 – 30.3 n = 5	0.3125
Stage 3-4 duration	24 ± 16 (19) 13 – 52 n = 5	18 ± 9 (17) 3 – 41	-8.8 ± 16.6 (-2.2) -37.0 – 6.0 n = 5	0.3125
REM duration	20 ± 9 (17) 11 – 35 n = 5	15 ± 4 (15) 8 – 23	-8.6 ± 11.7 (-6.1) -26.3 – 4.4 n = 5	0.1875

*If less than that supplied in column header.

[#]Wilcoxon signed rank test.

The pre-studies were performed two to five months before inclusion in the study (time lag three to eight months). They led to NIV in two cases, adjustments of NIV settings in one case, continuous positive airway pressure for obstructive sleep apnoea in one case, and no intervention in two cases.

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diaphragm pacing system. Raymond Onders owns equity in Synapse Biomedical Inc. and has intellectual property rights in the diaphragm pacing system. Case Western Reserve University and University Hospitals Case Medical Center also have equity and intellectual property rights in diaphragm pacing. Teresa Nelson is a part-owner of Technomics Research LLC, to which Synapse Biomedical Inc. paid per-hour fees for performing the statistical analysis. Fabrice Menegaux has been asked by Synapse Biomedical Inc. to train two other European surgeons in the implantation procedure, in exchange for which Synapse paid a subsidy to the non-profit research association to which Fabrice Menegaux belongs (4000 euros paid in 2010). Thomas Similowski received honoraria for the translation from English to French of the technical and users' manual of two respiratory neurostimulators (the 'Atrostim' in 2002 (Atrotech, Tampere, Finland) and the 'NeurRxDP4' in 2007 (Synapse Biomed., Oberlin, Ohio, USA)).

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[AQ4]

1 **References**

- 2
- 3 1. Louwerse ES, Visser CE, Bossuyt PM, Weverling GJ. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors. The Netherlands ALS Consortium. *J Neurol Sci.* 1997;152 (Suppl 1): S10-7.
- 4
- 5 2. Millul A, Beghi E, Logroscino G, Micheli A, Vitelli E, Zardi A. Survival of patients with amyotrophic lateral sclerosis in a population based registry. *Neuroepidemiology.* 2005;25:114-9.
- 6
- 7 3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med.* 2001;344:1688-700.
- 8
- 9 4. Zoccollella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Samarelli V, et al. Analysis of survival and prognostic factors in amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry.* 2008;79:33-7.
- 10
- 11 5. Bourke SC, Shaw PJ, Gibson GJ. Respiratory function vs. sleep-disordered breathing as predictors of QoL in ALS. *Neurology.* 2001;57:2040-4.
- 12
- 13 6. Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry.* 2006;77:390-2.
- 14
- 15 7. Gil J, Funalot B, Verschueren A, Danel-Brunaud V, Camu W, Vandenberghe N, et al. Causes of death among French patients with amyotrophic lateral sclerosis: a prospective study. *Eur J Neurol.* 2008;15:1245-51.
- 16
- 17 8. Similowski T, Attali V, Bensimon G, Salachas F, Mehiri S, Arnulf I, et al. Diaphragmatic dysfunction and dyspnoea in amyotrophic lateral sclerosis. *Eur Respir J.* 2000;15: 332-7.
- 18
- 19 9. Arnulf I, Similowski T, Salachas F, Garma L, Mehiri S, Attali V, et al. Sleep disorders and diaphragmatic function in patients with amyotrophic lateral sclerosis. *Am J Respir Crit Care Med.* 2000;161:849-56.
- 20
- 21 10. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2007:CD001447.
- 22
- 23 11. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. *Lancet Neurol.* 2006;5: 140-7.
- 24
- 25 12. Lechtzin N, Scott Y, Busse AM, Clawson LL, Kimball R, Wiener CM. Early use of non-invasive ventilation prolongs survival in subjects with ALS. *Amyotroph Lateral Scler.* 2007;8:185-8.
- 26
- 27 13. Tripodoro VA, de Vito EL. Management of dyspnoea in advanced motor neuron diseases. *Curr Opin Support Palliat Care.* 2008;2:173-9.
- 28
- 29 14. Cheah BC, Boland RA, Brodaty NE, Zoing MC, Jeffery SE, McKenzie DK, Kiernan MC. Inspirational-inspiratory muscle training in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2009;1-9.
- 30
- 31 15. Berto MC, Filha SC, Camelier A, Rosa FW, de Souza Bulle Oliveira A, Jardim JR. Acute action of aminophylline in patients with amyotrophic lateral sclerosis. *Acta Neurol Scand.* 2007;115:301-5.
- 32
- 33 16. Sheffler LR, Chae J. Neuromuscular electrical stimulation in neurorehabilitation. *Muscle Nerve.* 2007;35:562-90.
- 34
- 35 17. Scott OM, Hyde SA, Vrbova G, Dubowitz V. Therapeutic possibilities of chronic low frequency electrical stimulation in children with Duchenne muscular dystrophy. *J Neurol Sci.* 1990;95:171-82.
- 36
- 37 18. Handa I, Sihimizu H, Mimani H, Ihashi K, Yagi R, Matsushita N, et al. Long-term effects of therapeutic electrical stimulation for ALS patients. Proceedings of the 8th World Congress of the International Rehabilitation Medicine Association. 1997:1139-42.
- 38
- 39 19. DiMarco AF. Restoration of respiratory muscle function following spinal cord injury. Review of electrical and magnetic stimulation techniques. *Respir Physiol Neurobiol.* 2005;147:273-87.
- 40
- 41 20. Glenn WW, Holcomb WG, Shaw RK, Hogan JF, Holschuh KR. Long-term ventilatory support by diaphragm pacing in quadriplegia. *Ann Surg.* 1976;183:566-77.
- 42
- 43 21. Acker MA, Mannion JD, Brown WE, Salmons S, Henriksson J, Bitto T, et al. Canine diaphragm muscle after one year of continuous electrical stimulation: its potential as a myocardial substitute. *J Appl Physiol.* 1987;62:1264-70.
- 44
- 45 22. Marzocchi M, Brouillette RT, Klemka-Walden LM, Heller SL, Weese-Mayer DE, Brozanski BS, et al. Effects of continuous low-frequency pacing on immature canine diaphragm. *J Appl Physiol.* 1990;69:892-8.
- 46
- 47 23. Peterson DK, Nochomovitz ML, Stellato TA, Mortimer JT. Long-term intramuscular electrical activation of the phrenic nerve: safety and reliability. *IEEE Transactions on Bio-medical Engineering.* 1994;41:1115-26.
- 48
- 49 24. Bradley WG, Good P, Rasool CG, Adelman LS. Morphometric and biochemical studies of peripheral nerves in amyotrophic lateral sclerosis. *Ann Neurol.* 1983;14:267-77.
- 50
- 51 25. Culebras A. Sleep disorders and neuromuscular disease. *Semin Neurol.* 2005;25:33-8.
- 52
- 53 26. Steier J, Jolley CJ, Seymour J, Kaul S, Luo YM, Rafferty GF, et al. Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness. *Eur Respir J.* 2008;32: 1479-87.
- 54
- 55 27. Ferguson KA, Strong MJ, Ahmad D, George CF. Sleep-disordered breathing in amyotrophic lateral sclerosis. *Chest.* 1996;110:664-9.
- 56
- 57 28. Bennett JR, Dunroy HM, Corfield DR, Hart N, Simonds AK, Polkey MI, Morrell MJ. Respiratory muscle activity during REM sleep in patients with diaphragm paralysis. *Neurology.* 2004;62:134-7.
- 58
- 59 29. Onders RP, Carlin AM, Elmo M, Sivashankaran S, Katiariji B, Schilz R. Amyotrophic lateral sclerosis: the mid-western surgical experience with the diaphragm pacing stimulation system shows that general anaesthesia can be safely performed. *Am J Surg.* 2009;197:386-90.
- 60
30. Onders RP, Elmo M, Khansarinia S, Bowman B, Yee J, Road J, et al. Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. *Surg Endosc.* 2009;23:1433-40.
31. Onders RP, Dimarco AF, Ignagni AR, Aiyar H, Mortimer JT. Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. *Surgery.* 2004;136:819-26.
32. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report of working party standardization of lung function tests, European community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J Suppl.* 1993;16:5-40.
33. Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. *Thorax.* 1995;50: 371-5.
34. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis.* 1969;99:696-702.
35. Mills GH, Kyroussis D, Hamnegard CH, Polkey MI, Green M, Moxham J. Bilateral magnetic stimulation of the phrenic nerves from an anterolateral approach. *Am J Respir Crit Care Med.* 1996;154:1099-105.
36. American Thoracic Society, European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002;166:518-624.
37. Rechstchaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, CA, USA: UCLA Brain Information Service/Brain Research Institute; 1968.
38. American Sleep Disorders Association. EEG arousals: scoring rules and examples. A preliminary report from

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115
116
117
118
119
120

1	the sleep disorders Atlas task force of the American Sleep		
2	Disorders Association. <i>Sleep</i> . 1992;15:173–84.		
3	39. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM	45. Nuhr M, Crevenna R, Gohlsch B, Bittner C, Pleiner J,	61
4	manual for the scoring of sleep and associated events:	Wiesinger G, et al. Functional and biochemical properties	62
5	rules, terminology, and technical specification, 1st edn.	of chronically stimulated human skeletal muscle. <i>Eur J Appl</i>	63
6	Westchester, Illinois, USA; 2007.	<i>Physiol</i> . 2003;89:202–8.	64
7	40. Hochberg Y, Benjamini Y. More powerful procedures	46. Pette D. Fibre transformation and fibre replacement in	65
8	for multiple significance testing. <i>Stat Med</i> . 1990;9:811–8.	chronically stimulated muscle. <i>J Heart Lung Transplant</i> .	66
9	41. Erman MK, Zammit G, Rubens R, Schaefer K, Wessel T,	1992;11:S299–305.	67
10	Amato D, et al. A polysomnographic placebo-controlled	47. Nochomovitz ML, Hopkins M, Brodkey J, Montenegro H,	68
11	evaluation of the efficacy and safety of eszopiclone relative	Mortimer JT, Cherniack NS. Conditioning of the diaphragm	69
12	to placebo and zolpidem in the treatment of primary insom-	with phrenic nerve stimulation after prolonged disuse.	70
13	nia. <i>J Clin Sleep Med</i> . 2008;4:229–34.	<i>Am Rev Respir Dis</i> . 1984;130:685–8.	71
14	42. Roth T, Soubrane C, Titeux L, Walsh JK. Efficacy and safety	48. Dangain J, Vrbova G. Long-term effect of low frequency	72
15	of zolpidem-mr: a double-blind, placebo-controlled study in	chronic electrical stimulation on the fast hind limb muscles	73
16	adults with primary insomnia. <i>Sleep Med</i> . 2006;7:397–406.	of dystrophic mice. <i>J Neurol Neurosurg Psychiatry</i> . 1989;	74
17	43. Agnew HW Jr, Webb WB, Williams RL. The first-night effect:	52:1382–9.	75
18	an EEG study of sleep. <i>Psychophysiology</i> . 1966;2:263–6.	49. Kernell D, Eerbeek O. Recovery after intense chronic	76
19	44. Attali V, Mehiri S, Straus C, Salachas F, Arnulf I,	stimulation: a physiological study of cat's fast muscle. <i>J Appl</i>	77
20	Meininger V, et al. Influence of neck muscles on mouth	<i>Physiol</i> . 1991;70:1763–9.	78
21			79
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