On-line supplement - Polysomnography vs. Limited Respiratory Monitoring and Nurse-Led Titration To Optimise Non-Invasive Ventilation Set Up: A Pilot Randomised Clinical Trial

Material and methods

Subjects

Patients referred to the Lane Fox Respiratory Unit, St Thomas' Hospital, Guy's and St Thomas' Foundation Trust, London, UK for NIV setup with a background of COPD and suspected OSA were screened for eligibility. Inclusion criteria were a known diagnosis of COPD as defined by GOLD criteria [1], OSA defined by a 4% oxygen desaturation index > 7.5 events/hour or an apnoea-hypopnea index > 5/hours, a daytime $PaCO_2$ > 6kPa and a body mass index (BMI) > 30kg/m^2. Exclusion criteria were decompensated respiratory failure with a pH < 7.35, inability to tolerate NIV (< 4 hours usage during titration), contraindication to NIV, pregnancy, age < 18 years and any significant physical or psychiatric co-morbidity that would prevent compliance with the trial protocol. Written consent was obtained for all eligible patients.

Study design

The study was an open-label, single-centre randomised clinical trial. Patients were allocated to have NIV setup with an overnight titration using a full montage polysomnography (PSG) or using attended limited respiratory monitoring with transcutaneous oxi-capnometry and protocol-based titration (LRM). Randomisation was performed using dedicated software with minimisation based on gender and use of long term oxygen therapy (LTOT).

Study protocol

The trial was registered and submitted on clinicaltrial.gov prior to patient recruitment. For administrative reasons, the study was not released until 12th May 2015. Study protocol remained unchanged.

All included patients underwent baseline spirometry, daytime arterial blood gas sampling, overnight inpatient study using combined transcutaneous oxi-capnometry (Tosca 500, Radiometer, Crawley, UK) and baseline respiratory polygraphy (Embletta, Resmed, Abingdon, UK). Anthropometrics: weight, height, BMI, neck circumference were collected. Subjects were asked to complete health related quality

of life questionnaires: COPD Assessment Test (CAT), Pittsburgh Sleep Quality Index (PSQI) [2] and Severe Respiratory Insufficiency questionnaire (SRI) [3,4]. Subjects were asked to assess their breathlessness using the modified Medical Research Council dyspnoea score and Borg Scale and their sleepiness using Epworth Sleepiness Scale (ESS). Quality of sleep and of overnight breathing during baseline sleep study and during overnight titration was assessed using visual analogue scales (VAS) (0: very easy / comfortable – 100: very difficult / uncomfortable). Comfort of breathing and breathlessness were assessed on NIV using the same VAS. All patients were initiated on NIV in the Lane Fox Respiratory Unit in which they received the same structured training for home NIV use.

Overnight NIV titration was performed using A30 ventilators (Philips-Respironics, Murrysville, Pennsylvania, USA) on spontaneous-timed mode with an oro-nasal interface adjusted to optimise comfort and minimise unintentional leaks (Quattro, Quattro FX and Airfit F10 masks (Resmed, Abingdon, UK)).

For patients randomised to the limited respiratory monitoring, overnight titration was performed using a nurse-led protocol (*Figure E1*) based on transcutaneous oxi-capnometry signal and clinical examination. All titrations were performed by trained nurses with clinical observation at the bedside performed at least every 30 minutes. Not all titrations were performed by the same nurse. Overnight titration aimed to achieve sufficient control of apnoeic events and of hypoventilation. This assessment was performed by a consultant with a special interest in respiratory failure and home mechanical ventilation. Assessment of ventilation was based on the results of the oxi-capnometry monitoring, nursing notes regarding the overnight titration and their clinical assessment.

For patients randomised to PSG led NIV setup, all overnight titration were performed by a chest physician (MP) with the guidance of polysomnography (ALICE 5; Philips-Respironics, Murrysville, PA, USA) with continuous recording of electro-encephalogram (EEG), electro-oculogram (EOG), submental electromyogram (EMG), anterior tibialis EMG, oxygen saturation (SpO_2), electrocardiogram (ECG), pulse rate, mask pressure, respiratory inductance plethysmography (thoracic and abdominal) and transcutaneous oxi-capnometry (Tosca 500, Radiometer, Crawley, UK) and clinical examination. Overnight titration aimed to abolish apnoeic events, control nocturnal hypoventilation and minimise patient-ventilator asynchronies. Polysomnographic analysis of sleep was performed using ASM guidelines [5]. Polysomnographic analysis of respiratory events was performed according to SomnoVNI guidelines [6]. Patient-ventilator asynchronies were defined as follows: auto-triggering (breath delivered

by ventilator in the absence of any respiratory effort at a different rate from the set back-up rate), multiple triggering (repeated (at least once) breaths delivered by the ventilator associated with shorten inspiratory time and desynchronization from patient respiratory efforts), ineffective triggering (presence of an inspiratory and expiratory respiratory movement not associated with any pressure delivery by the ventilator), trigger delay (breath delivered by ventilator after more than 25% of the inspiratory effort produced by the patient), early cycling (interruption of pressure generation despite the persistence of an inspiratory effort produced by the patient), late cycling (maintenance of pressure to IPAP level despite initiation of expiration by the patient), and leaks (sudden loss of mask pressure during expiration or inspiration resulting in more than 25% reduction of the pressure) [7]. Given the study design, patient ventilator asynchronies could only be assessed in the PSG arm. Analysis was performed in 30s-epochs, if an apnoea occurred during an epoch the period was scored as apnoeic. In the absence of an apnoeic event the epoch was examined for evidence of patient ventilator asynchrony. Only one patient ventilator asynchrony was scored per epoch. If multiple asynchronies occurred in a single epoch, the predominant asynchrony was scored. Frequency of patient ventilator asynchrony (PVA) was calculated for each NIV setting used during the titration process. For patients in the PSG arm, home settings were further adjusted before discharge according to results from the full PSG analysis. Chosen settings were those under which the patient had satisfactory control of sleep disordered breathing with lowest level of PVA. Patients were discharged once satisfactory control of sleep disordered breathing was obtained, as determined by the supervising consultant. If after the first night, the supervising consultant judged that control of sleep disordered breathing was insufficient, patients had a further titration night with the same monitoring as their first night. Following discharge, patients completed a sleep diary that included subjective assessment of sleep quality (1: poor, 2: average, 3: good) for 2 weeks. Objective sleep quality was assessed by 2-week wrist worn actigraphy (Actiwatch spectrum; Philips, Murrysville, PA, USA) at 3 month follow up.

Patients attended a 6 weeks outpatient follow-up as part of standard care to optimise NIV compliance. Final follow-up was performed at 3 months with baseline measures repeated.

Nested physiological study

After NIV initiation, all patients underwent an assessment of their pulmonary mechanics including: sniff nasal inspiratory pressure (snip), maximal inspiratory pressure (mip), maximal expiratory pressure

(mep), forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC), vital capacity (VC) and self-ventilating tidal volume (Vt). During respiratory manoeuvres, neural respiratory drive (NRD) was measured using surface electrodes applied in the parasternal area of the second intercostal space (EMGpara) as previously described [8]. A measurement of EMGpara was also performed whilst on NIV. Unloading of the respiratory muscles was calculated [(EMGpara on NIV – EMGpara during tidal breathing)/EMGpara during tidal breathing] and expressed as percentage change [9]. All physiology measurements were performed in line with ATS/ERS guidelines [10]. Data were acquired using an analogue to digital converter (Powerlab, ADInstuments, Chalgrove, UK) and analysed using specialist software (Labchart v7.2, ADInstuments, Chalgrove, UK).

Statistical analysis

Based on prior results from our group [11] in a similar population, we designed this pilot study to include 12 patients. To allow for a dropout rate of 15%, we targeted 14 patients for randomisation and 14 patients were analysed.

Normal distribution was assessed by visual inspection and using the Shapiro-Wilks test. Results are expressed as number and percentages, means and standard deviation (SD) when normally distributed or medians, and inter quartile range (IQR) when not normally distributed. Estimates of effect size are provided with 95% confidence intervals (95%CI) but due to the small sample size inferential statistics were not employed on the clinical study. The nested physiological study used paired and unpaired t-test or non-parametric alternative as appropriate for comparison using a level of 0.05 to denote significance. Correlations were assessed using the Spearman correlation coefficient. The analyses were performed using GraphPad Prism 6® for Mac OS X® (GraphPad Software, La Jolla, CA, USA) and IBM SPSS® Statistics v20.0 (IBM Corp, Armonk, NY, USA).

Ventilation setup and nested physiological study

Results

NIV titration

Length of stay for baseline assessments and NIV setup was similar between both groups: 2 [2 – 2] nights in the limited arm vs. 2 [2 – 3] nights and the PSG arm. NIV settings were similar between both groups with comparable rate of control of sleep breathing disorder, although with a trend to higher EPAP

in the PSG arm (*Table E1*). PSG monitoring for overnight titration did not significantly altered the perceived ease of sleep onset or sleep comfort as compared to limited monitoring. Overnight comfort of breathing on NIV was similar in both groups (*Table E1*).

PSG results

Subjects in the PSG arm had a median duration of sleep of 307min [201 – 431]. Duration and proportion of N1, N2, N3 and REM sleep were 35min [3 – 43] (9%), 161min [140 – 234] (74%), 11min [0 – 85] (5%), 9min [4 – 19] (5%), respectively. Median arousals occurrence was 12.1 [6.6 – 20.3] per hour. During overnight titration, residual AHI was 14.6±16/hour with the majority of events occurring prior to achieving final therapeutic pressure (*Table E2*). Mean PVA occurrence was 27.2±19.4/hour. PVA were associated with a 3% desaturation in 278 (15%) epochs and with an arousal in 195 (11%) epochs. Predominant type of PVA varied for each patient (*Table E3*). Incidence of PVA and residual apnoeic events was significantly lower when subjects were ventilated using final therapeutic settings as compared to the rest of the night: 19.3±14.9 vs. 35.4±18.2 (p=0.0045) (*Figure E3*). For the patients in PSG arm, there was no significant correlation between the frequency of PVA and compliance (p=0.071).

Nested physiological study

There was no significant difference between groups with respect to their respiratory muscle strength (*Table E4*). Although raw EMGpara during self-ventilation was similar between groups, once normalised for maximum muscle strength, subjects in the PSG arm used a higher proportion of their NRD during tidal breathing than those in the limited arm. In the total study population, fall in NRD from self-ventilation to NIV (respiratory muscle offload) was correlated with NIV adherence (rho = -0.581, p=0.029) (*Figure E4*). At a cut-off value of 20%, NRD offloading was able to identify patients with a compliance below 3 hours/day with a sensitivity of 80%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 90%.

Discussion

Value of PSG during titration

As previously described in COPD population [12] and reflecting the complexity of ventilation management in COPD-OSA overlap, PVA are frequent. Whilst PVA appear deleterious during acute

NIV [13], their consequences during long-term NIV are not clear. Fanfulla *et al* reported a lower control of $PaCO_2$ in stable patients established on home NIV with high PVA. However, this impact was only found in patients experiencing more than 100 PVA/hour, in a heterogeneous population and with low pressure ventilation in patients with COPD alone [14]. In patients admitted for overnight NIV titration, no correlation was found between PVA and control of $PaCO_2$ [15]. Ramsay et al demonstrated a similar incidence of PVA to Fanfulla and colleagues [14]. In line with previous data, the most frequent PVA was ineffective triggering [14,15] but interestingly, each of the seven patients randomised to PSG setup had a different predominant type of PVA. Variability in PVA can be explained by the use of different ventilators [16], but in this study the same ventilator was used for all the patients in the trial, therefore this variability is likely explained by patients intrinsic characteristics.

Relevance of neural respiratory drive for NIV setup

Use of neural respiratory drive provides physiologically coherent and clinically useful data in COPD patients [17,18] and in patients with OSA [19] undergoing CPAP therapy [20,21]. Neural respiratory drive can be assessed easily and non-invasively using parasternal EMG [8,9,15,22]. In the overall study population, we have seen that an offload of respiratory muscle activity during NIV was associated with improved adherence to NIV. The use of EMGpara could allow identification of patients at risk of poor adherence and thus offer the opportunity to assess whether targeted support to the most at risk patients would improve subsequent adherence. Patients randomised to the PSG arm trended to have a higher EPAP when compared to those in the limited respiratory monitoring arm. We hypothesise that this higher EPAP resulted in a higher degree of hyperinflation leading to discomfort, as suggested by a higher EMGpara activity and to a lower compliance in that group. In that context, lack of offload of respiratory muscles may reflect hyperinflation caused by EPAP. In patients with COPD-OSA overlap, this physiological assessment is particularly relevant given the dose response to therapeutic efficacy demonstrated in this group [23].

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Figure E1: Nurse led protocol for NIV titration in COPD-OSA overlap patients (COPD-OSA: Chronic obstructive pulmonary disease and obstructive sleep apnoea, ST: spontaneous timed, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure, Ti: inspiratory time, BUR: back-up rate, TcCO2: transcutaneous carbon dioxide, Sat 02: Oxygen saturation)

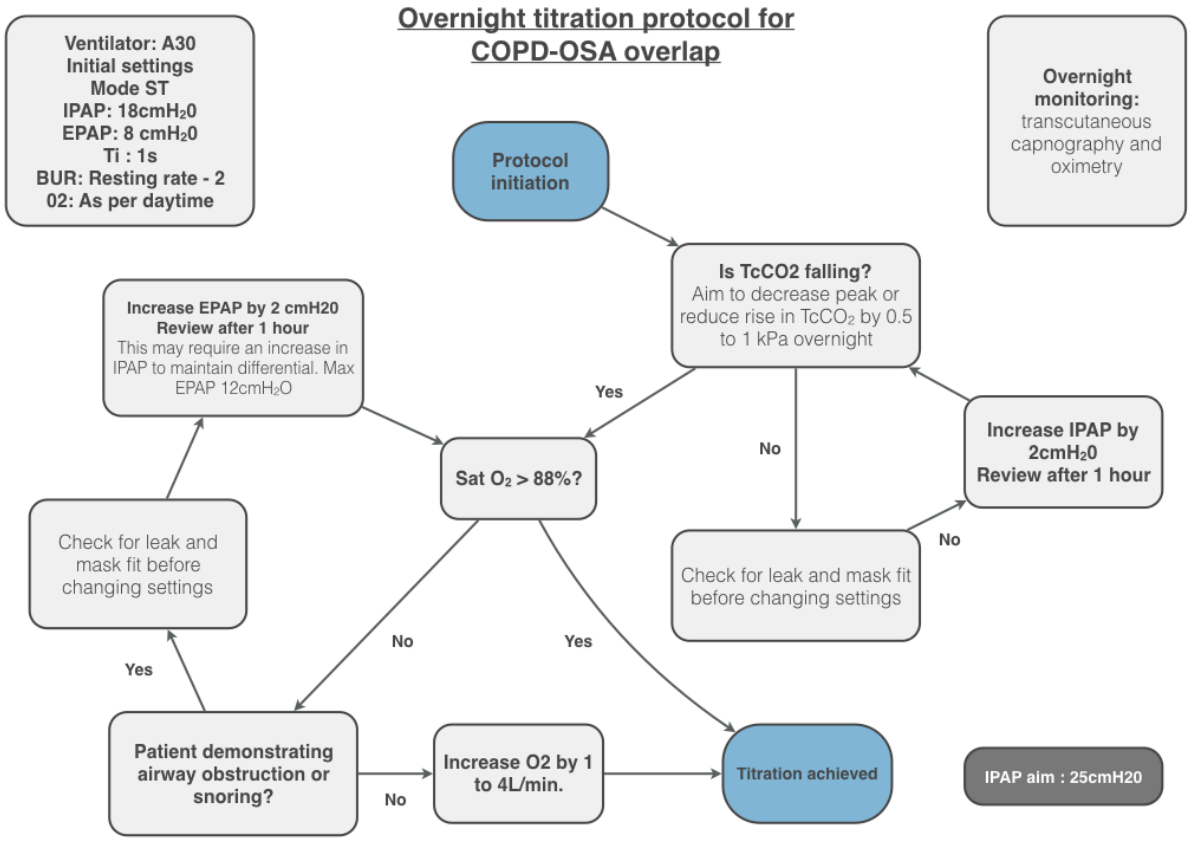

Figure E2: Consort recruitment diagram for enrolment and follow-up. (OSA: obstructive sleep apnoea, BMI: body mass index – NIV: non-invasive ventilation - PSG: polysomnography)

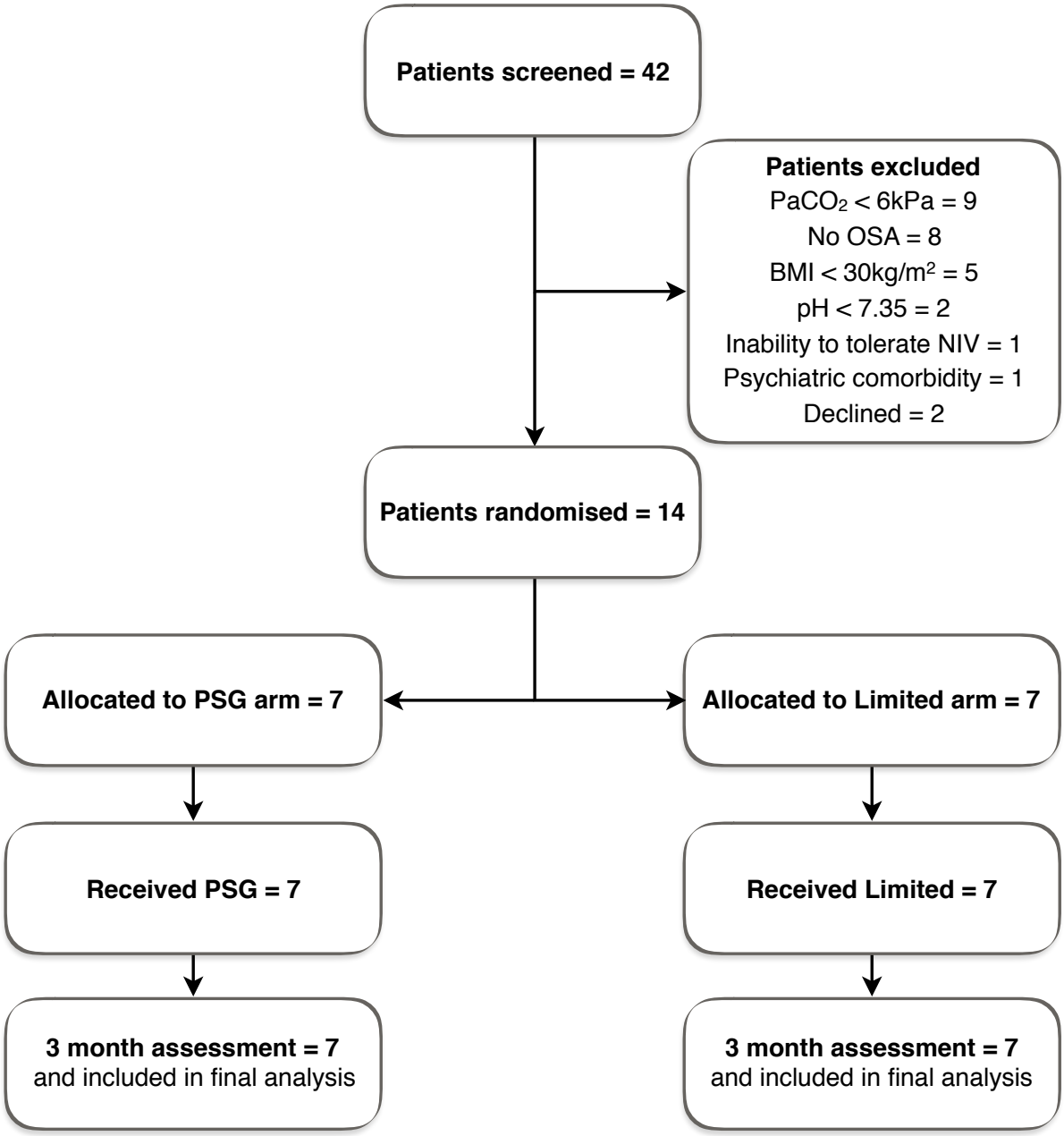

Figure E3: Frequency of PVA during overnight titration and on discharge settings (p=0.0045) (PVA: patient-ventilator asynchrony)

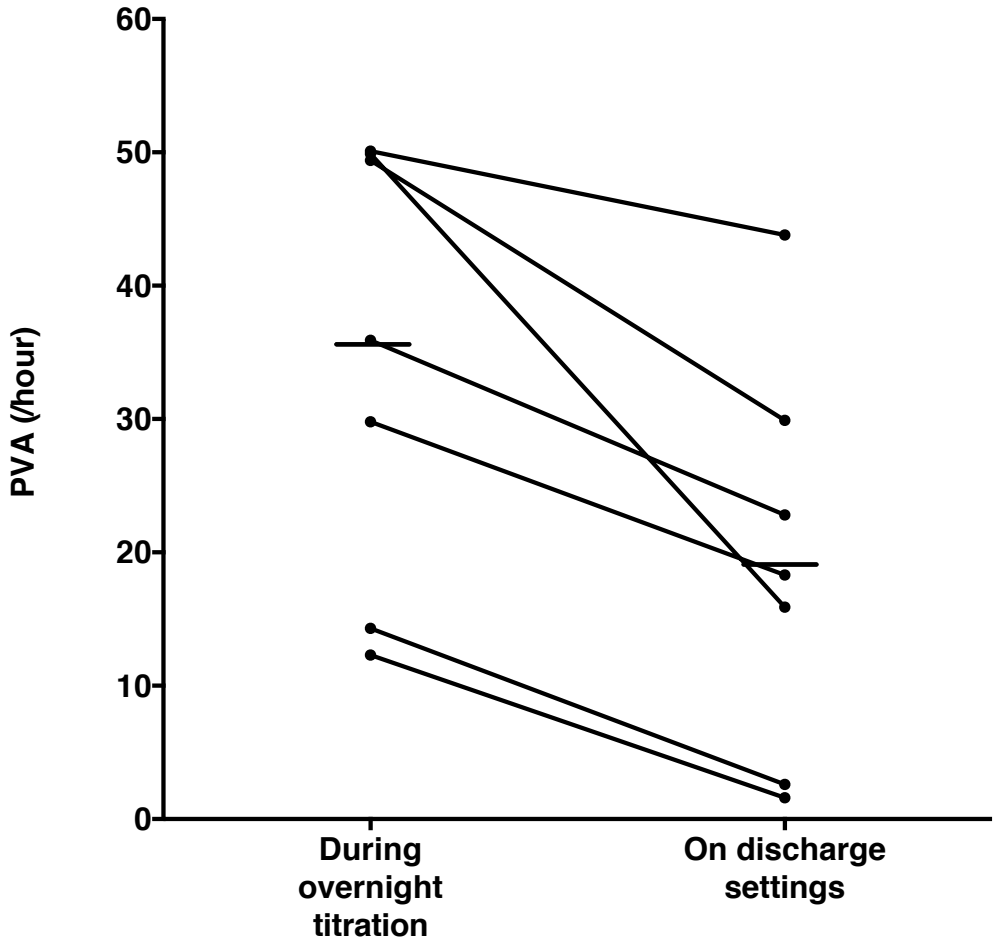

Figure E4: Correlation between offload of respiratory muscles and adherence to NIV (rho:-0.581, p:0.029) (NIV: noninvasive ventilation, EMGparasternal: parasternal surface electromyography)

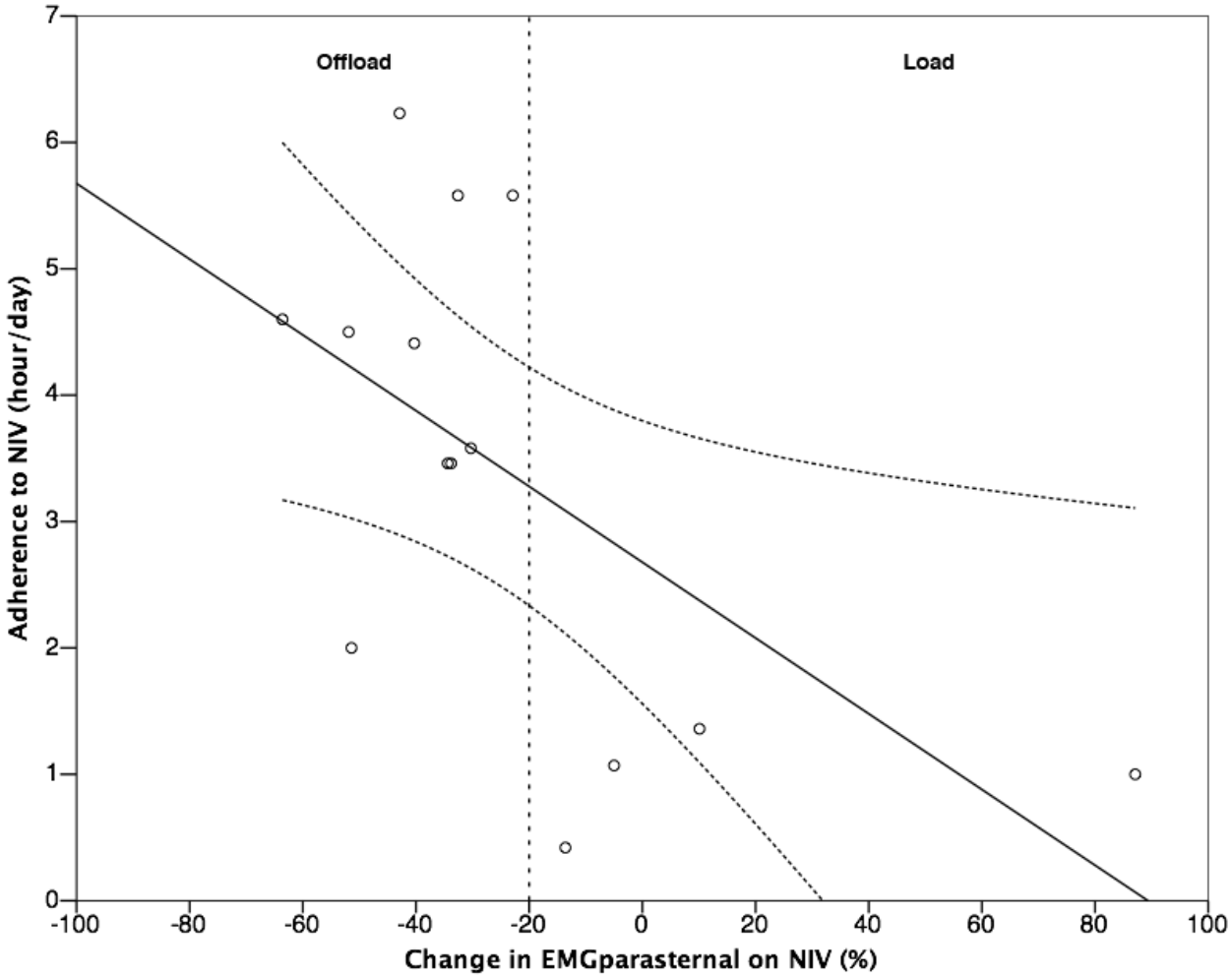

Table E1: Results from overnight NIV titration.

	Total	LRM	PSG	p
NIV settings at discharge				
IPAP (cmH2O)	25.8 (±2.9)	25.7 (±3.5)	26.0 (±2.3)	0.66
EPAP (cmH2O)	10 (±1.9)	9.1 (±1.9)	10.9 (±1.6)	0.17
Pressure support (cmH2O)	15.9 (±2.9)	16.6 (±2.8)	15.1 (±3)	0.37
BUR (/min)	15.7 (±1.7)	15.1 (±1.1)	16.3 (±2.1)	0.45
Ti (s)	1.06 (±0.1)	1.06 (±0.1)	1.06 (±0.1)	1
Overnight sleep monitoring during NIV titration*				
4% oxygen desaturation index (/h)	18.1 (±8.9)	19 (±6.6)	17.2 (±11.3)	0.68
Mean saturation O2 (%)	90.6 (±2.7)	89.8 (±2.9)	91.5 (±2.3)	0.3
Percentage of time spent < 90%	31.7 (±22)	35.1 (±26)	28.4 (±18.6)	0.78
Mean TcCO2 (kPa)	7.34 (±0.7)	7.33 (±0.7)	7.35 (±0.7)	1
Sleep quality during titration				
Easiness to fall asleep (0: very easy to 100: very difficult)	29.9 (±25)	22.1 (±22.7)	37.6 (±26.6)	0.26
Comfort of sleep (0: very uncomfortable to 100: very comfortable)	36.5 (±24.1)	38.7 (±26)	34.3 (±23.5)	0.75
Comfort of breathing overnight on NIV (0: very uncomfortable to 100: very comfortable)	37.9 (±24.2)	44.1 (±24.7)	31.7 (±26)	0.37

*Results are expressed in terms of mean (standard deviation) and number (percentage) *Whole night results including initial NIV settings through to optimal discharge settings. (LRM: protocol-based titration, PSG: polysomnography, NIV: noninvasive ventilation, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure, Ti: inspiratory time, BUR: back-up rate, TcCO2: transcutaneous carbon dioxide, Sat 02: Oxygen saturation)*

Table E2: Results of polysomnography performed during NIV overnight titration.

	Sleep staging						
	Sleep duration min	N1 min (%)	N2 min (%)	N3 min (%)	REM Min (%)	Arousals per hour (/hour)	Residual AHI (/hour)
Patient 1	478	376 (79%)	23 (5%)	0 (0%)	79 (16%)	27.1	2.7
Patient 2	432	37 (9%)	392 (90%)	3 (1%)	0 (0%)	5.6	41
Patient 3	244	43 (18%)	182 (74%)	11 (5%)	9 (3%)	25.8	2.8
Patient 4	201	3 (1%)	148 (74%)	42 (21%)	9 (4%)	14.7	3.4
Patient 5	307	15 (5%)	161 (52%)	116 (38%)	16 (5%)	7.5	31.3
Patient 6	144	0 (0%)	140 (97%)	0 (0%)	4 (2%)	12.1	4
Patient 7	372	35 (9%)	234 (63%)	85 (23%)	19 (5%)	4.2	7.5

Results are expressed in terms of mean and/or percentage. (NIV: noninvasive ventilation, REM: rapid eye movement, AHI: apnoea-hypopnoea index)

Table E3: Patient-ventilator asynchrony during NIV overnight titration in the PSG group.

	PVA per hour	Arousals related to PVA n (%)	Typology of patient-ventilator asynchrony per patient						
			Auto-triggering	Multiple triggering	Early cycling	Ineffective triggering	Late cycling	Leaks	Trigger delay
Patient 1	31.5	79 (34%)	6 %	16 %	13 %	21 %	12 %	7 %	26 %
Patient 2	22.6	25 (63%)	46 %	19 %	6 %	5 %	3 %	18 %	3 %
Patient 3	9.4	9 (9%)	7 %	73 %	0 %	10 %	11 %	0 %	0 %
Patient 4	65.8	33 (67%)	4 %	13 %	0 %	72 %	3 %	0 %	9 %
Patient 5	12.6	16 (41%)	17 %	21 %	14 %	10 %	9 %	24 %	6 %
Patient 6	51.2	13 (45%)	2 %	40 %	0 %	8 %	46 %	3 %	1 %
Patient 7	13	4 (15%)	9 %	29 %	1 %	12 %	48 %	1 %	0 %

Results are expressed in terms of mean and/or percentage. (PVA: patient-ventilator asynchrony)

Table E4: Neural respiratory drive and respiratory muscle strength assessment.

	Total	LRM	PSG	p
Respiratory muscle strength				
Sniff Nasal Inspiratory Pressure (cmH_20)	55.7 (±17.7)	62.6 (±19)	53.2 (±16.6)	0.34
Maximal Inspiratory Pressure (cmH_20)	54.6 [41.2 – 66.4]	63.9 [41.2 – 66.4]	49.2 [27 - 56.6]	0.16
Maximal Expiratory Pressure (cmH_20)	-98 (±33.3)	103.8 (±27.7)	86.8 (±8)	0.33
Neural Respiratory Drive				
EMGpara during tidal breathing (µV)	8.3 (±2.7)	8.0 (±1.8)	8.1 (±2.8)	0.96
EMGpara%max (%)	17.1 (±7.2)	12.8 (±4.3)	20.6 (±7.5)	0.033
EMGpara during NIV (µV)	5.3 [4.6 - 6.7]	5.4 [3.8 - 7]	5.2 [4.7 - 7.7]	0.47
Change in EMGpara from tidal breathing to NIV (%)	-23.4 (±39.7)	-32.8 (±15.3)	-13.7 (±50.6)	0.36

Results are expressed in terms of mean (standard deviation), median [interquartile] and number (percentage). (LRM: protocol-based titration, PSG: polysomnography, EMGpara: parasternal surface electromyography, NIV: noninvasive ventilation).