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Safety and efficacy of auto-titrating noninvasive ventilation in COPD and obstructive sleep apnoea overlap syndrome

To the Editor:

The deleterious effects of comorbid chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) have long been recognised and are frequently encountered as a clinical scenario [1, 2]. Although continuous positive airways pressure can be used in order to abolish upper airways obstruction in OSA, it can have adverse effects on pulmonary mechanics in patients with airways obstruction [3]. Auto-titrating modes of noninvasive ventilation (NIV) that monitor tidal volume, respiratory rate and upper airway patency and can vary back up rate, inspiratory and expiratory positive airway pressure (IPAP and EPAP, respectively) may have clinical benefits. However, these auto-titration modes and the software algorithms driving the ventilators are being engineered and modified at a rapid rate. The clinician, therefore, needs to be reassured that these novel modes have an established safety and efficacy profile. We hypothesised that auto-titrating NIV would enhance overnight gas exchange, sleep quality, and patient comfort when compared to standard fixed-level NIV in COPD-OSA patients with chronic respiratory failure.

A phase 2 open-labelled sequential treatment design recruited patients from two established home ventilation centres. 10 patients were required to achieve a power of 80% at a p=0.05, assuming a standard deviation of 0.5 kPa, to demonstrate a 0.5 kPa difference in mean nocturnal transcutaneous carbon dioxide tension (P_{tcCO_2}) from fixed to auto-titrating NIV. Local research ethics approval was obtained (11/LO/1627) and the trial was registered on the ClinicalTrials.gov database with identifier number: NCT01601977.

Ten patients established on NIV for hypercapnic respiratory failure secondary to COPD-OSA overlap syndrome were recruited. Patients were excluded if they had had recent upper airway, nose or sinus surgery in the 90 days prior to the study entry or an untreated non-respiratory sleep disorder.

Patients underwent baseline measures at study entry on fixed-level NIV [4]. Arterial blood gas analysis was performed at least 4 h after waking in a seated position without supplementary oxygen. Patients attended for assessment of clinical stability at the start of the trial and then underwent 14-day home actigraphy [5] prior to admission for baseline assessment and full polysomnography [6] on their usual NIV device. The following day patients were acclimatised to the auto-titrating NIV device (average volume assured pressure support – auto EPAP algorithm delivered *via* the Omnilab device; Philips-Respironics, Murrysville, PA, USA) prior to undergoing a repeat polysomnography on auto-titrating NIV. Patients were discharged with home actigraphy monitoring. Patients returned for a single night oximetry capnography to ensure clinical stability at day 28. End of study assessments were conducted on day 56 along with repeat polysomnography.

The auto-titrating device was set with a target volume of 10 mL per kg ideal body weight ($23\times height^2$) to deliver a pressure support of 4–26 cmH_2O, with an EPAP of 4–14 cmH_2O. The device was limited to a maximum IPAP of 30 cmH_2O. The auto-titrating device performed breath by breath titration of pressure support to achieve preset target volume and EPAP to maintain upper airway patency. The automatic backup rate was limited between 10 and 20 and set nightly by the ventilator at the average resting breathing rate of the patient during the first hour of therapy, minus two breaths per minute. Oxygen was entrained at the usual flow rate for the individual subject. During the titration night on auto-titrating NIV, if there was sustained hypoxia the target volume could be increased up to 12 $mL\cdot kg^{-1}$ at the discretion of the attending physician.

The primary outcome of the study was pre-specified as mean overnight $P_{tc}CO_2$ at the end of the study visit. Data were inspected for normality and end-points, which were not normally distributed, were appropriately transformed to fit the assumptions of a repeated-measures ANOVA model. *Post hoc* comparisons were performed using a Bonferroni correction on end-points showing an overall significant treatment effect.

10 clinically stable COPD-OSA overlap patients (seven male and three female) established on NIV using attended respiratory polygraphy for at least 6 months were recruited. Patients had a mean±SD age of 63±8 years with a mean±SD forced expiratory volume in 1 s of 965±533 mL (34±13% pred). Arterial blood gas analysis confirmed hypercapnic respiratory failure (mean±SD arterial carbon dioxide tension (P_aCO_2), arterial oxygen tension (P_aO_2) and bicarbonate were 7.0±2.0 kPa, 8.2±2.0 kPa and 30±6 $mmol\cdot L^{-1}$, respectively) at enrolment. Baseline anthropometrics showed a mean±SD body mass index (BMI) and neck circumference of 33±8 $kg\cdot m^{-2}$ and 42±6 cm, respectively. Auto-titrating NIV maintained overnight gas exchange compared to the fixed-level NIV at night 15, 28 and 56 (table 1).

There were no changes in objective sleep quality following transition from fixed-level to auto-titrating NIV measured by either polysomnography or actigraphy [7]. However, there was an improvement in subjective sleep comfort measured by visual analogue scale (p=0.027), which increased from first to last visit (Δ12 mm, 95% CI 3–21 mm; p=0.013). Ventilator adherence increased over the course of the study (p=0.010) with an increase observed by day 14 (Δ126 min, 95% CI 9–243 min; p=0.035). There were no further improvement by day 56 (Δ22 min, 24−68 min; p=0.574).

There was no change in daytime gas exchange, P_aCO_2 (p=0.680), P_aO_2 (p=0.438) or bicarbonate (p=0.961) during follow-up. The automated algorithm produced similar ventilator settings throughout the study period compared to the fixed-level setting with trends towards lower pressure support (p=0.155) and higher EPAP (p=0.085).

Patients had impaired health-related quality of life at study onset with a COPD Assessment Test (CAT) score of 21±4, a Severe Respiratory Insufficiency Summary Score (SRI-SS) of 58±16 and an Epworth Sleepiness Score (ESS) of 8±4 with no changes observed in CAT score (p=0.172), SRI-SS (p=0.703) and ESS (p=0.548). An improvement was demonstrated in the respiratory complaints subscale of the SRI at day 56 (Δ9, 95% CI 1–17; p=0.029).

This study represents the first report of the application of an auto-titrating NIV device with an algorithm that continually monitors and measures target volume, upper airways patency and respiratory rate to modify the IPAP, EPAP and back-up rate settings of the ventilator in order to optimise the delivery of NIV. Auto-titrating NIV provided effective control of sleep disordered breathing and nocturnal hypoventilation, with titration achieved in a single night producing similar settings to those of fixed-level devices achieved by previously attended respiratory polygraphy. In addition, there was no difference in sleep quality but ventilator adherence and subjective sleep comfort were improved during auto-titrating NIV.

The primary goal of the current study was to investigate the control of sleep disordered breathing. The data demonstrates clinical parity between established fixed-level pressure support and auto-titrating NIV.

TABLE 1 Sleep and ventilation outcome parameters for fixed-level and auto-titrating noninvasive ventilation (NIV) at mid-point and end of trial assessments

	Fixed-level NIV		Auto-titrating NIV		p-value
	Day 14	Day 15	Day 28	Day 56	
Mean P_{tcCO_2} kPa	6.5±1.6	6.9±1.4	6.5±1.8	6.7±1.4	0.568
Max P_{tcCO_2} kPa	7.8±2.2	8.5±2.3	7.5±2.0	7.7±1.5	0.433
4% oxygen desaturation index events·h^{-1}	15±15	11±9	7±8	16±27	0.356
Mean S_{pO_2} %	92±5	94±3	94±3	93±3	0.111
Total sleep time <90% %	30±31	18±28	5±9	21±28	0.153
Set estimated tidal volume mL		608±105			
Minute ventilation$^{\#}$ L·min^{-1}			9.8±2.6	9.5±2.4	
Pressure support$^{\#}$ cmH_2O	18±7		15±3	15±3	0.155
EPAP$^{\#,¶}$ cmH_2O	8±4		11±2	11±2	0.085
Respiratory rate$^{\#,+}$ bpm	12±3		15±3	15±3	
Daily use$^{\#}$ h:min	6:21±2:02		8:27±1:31	8:05±1:06	0.010
Total sleep time min	306±77	389±68		330±71	0.078
NREM 1 min	50±56	45±18		34±21	0.461
NREM 2 min	133±52	183±69		147±33	0.121
NREM 3 and 4 min	73±31	82±41		89±51	0.492
REM min	50±21	79±33		61±26	0.066
Wake after sleep onset min	171±54	122±30		155±65	0.172
Sleep efficiency %	57±11	67±9		61±11	0.144
Apnoea–hypopnoea index events·h^{-1}	5±6	5±8		3±4	0.445
Arousals events·h^{-1}	25±10	30±13		23±7	0.218

Data are presented as mean±SD, unless otherwise stated. P_{tcCO_2}: transcutaneous carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; EPAP: expiratory positive airway pressure; NREM: non-rapid eye movement; REM: rapid eye movement. The p-value refer to analysis by repeated measures of ANOVA. $^{\#}$: ventilator data refer to mean data for period from either baseline or previous visit to study day; ¶: EPAP on fixed-level reflects set pressure and on auto-titrating device reflects 90th percentile delivered EPAP; $^{+}$: respiratory rate on fixed-level reflects set backup rate and on auto-titrating device actual respiratory rate.

In terms of clinical safety, the control of nocturnal carbon dioxide levels was identified as an important end-point as it has been shown to correlate well with improvements in daytime gas exchange, the principal goal of NIV [8].

The control of sleep disordered breathing was maintained following the transfer from a fixed-level to an auto-titrating device from the first night of titration to day 28 and at day 56 with similar settings adopted by the automated device compared to fixed-level therapy. Importantly, all patients had adequate control established on the first night without the need for further titration nights and ventilator adjustments. However, the trend to a reduction in pressure support and an increase in expiratory pressure was achieved with oxygenation and nocturnal hypoventilation maintained, which wholly reflects the combined goal of NIV to optimise upper and lower airways pressurisation, facilitating gas exchange, as well as maximising patient comfort. When establishing ventilator settings in COPD-OSA patients, a balance must be achieved between the control of upper airway collapse and lower airways obstruction, without adversely affecting lung hyperinflation. This can lead to an increase in pressure support in order to overcome the altered pulmonary mechanics that occur with lung hyperinflation with the resting position of the respiratory system being positioned at a superior part of the pressure–volume curve [9, 10]. Indeed, it has previously been shown that a decrease in pressure support in COPD patients established on NIV, albeit without OSA, produces an improvement in morning dyspnoea and subjective sleep quality [11]. This study by Adler *et al.* [11] used polysomnography to optimise NIV settings in eight patients and demonstrated a reduction in pressure support with a subsequent increase in spontaneous respiratory rate, to maintain minute ventilation, which mirrored the automated changes in ventilator settings observed in the current study. This may have resulted in the improvement in the respiratory complaints subdomain observed during the study.

These current data support the previous data by Murphy *et al.* [5], which demonstrated that the application of auto-titrating devices is not associated with a worsening of sleep quality. In addition, the auto-titrating NIV device demonstrated clinical safety and efficacy comparable to standard fixed-level therapy and augmented sleep comfort and ventilator adherence. These novel data warrant further prospective investigation.

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Auto-titrating NIV controls sleep disordered breathing and augments patient sleep comfort in COPD-OSA overlap http://ow.ly/NtL24

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