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ORIGINAL ARTICLE

Automatic EPAP intelligent volume-assured pressure support is effective in patients with chronic respiratory failure: A randomized trial

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ABSTRACT

Background and objective: **Patients with chronic respiratory failure are increasingly managed with domiciliary non-invasive ventilation (NIV). There may be limited ability to provide NIV titration for these complex patients, and ventilatory requirements and upper airway support needs may change over time. Therefore, an automatically adjusting expiratory positive airway pressure (AutoEPAP) algorithm may offer advantages over manually adjusted EPAP for treating these patients. This study compared 4% oxygen desaturation index (ODI4%) values during the use of an AutoEPAP algorithm versus manual EPAP titration with the intelligent volume-assured pressure support (iVAPS) algorithm.**

Methods: **This prospective, single-blind, randomized, crossover study was conducted at six US sites. Patients with chronic respiratory failure (neuromuscular disease, chronic obstructive pulmonary disease, obesity hypoventilation and other aetiologies) and an apnoea–hypopnoea index of >5/h who were already established NIV users underwent a single night of NIV with the iVAPS manual EPAP and iVAPS AutoEPAP in the sleep laboratory in random order.**

Results: **A total of 38 patients constituted the study population. Mean ODI4% was statistically non-inferior with AutoEPAP versus manual EPAP ($P < 0.0001$). There was no difference in the effect on ODI4% across respiratory failure subgroups. Ventilation parameters and gas exchange were similar with either NIV mode, indicating equally effective treatment of respiratory failure. Sleep parameters were improved during AutoEPAP versus manual EPAP.**

Conclusion: **A single night of NIV using the iVAPS with AutoEPAP algorithm was non-inferior to a single night of iVAPS with manual EPAP titration in patients with respiratory failure.**

SUMMARY AT A GLANCE

Automated expiratory positive airway pressure (EPAP) titration may be helpful in treating patients with respiratory failure and upper airway obstruction. This study demonstrates that, for a single night's titration, an automated EPAP algorithm is as effective as manually set EPAP for treating desaturation, without compromising ventilation and potentially improving sleep quality.

Clinical Trial Registration: NCT02683772 at clinicaltrials.gov

Key words: chronic obstructive pulmonary disease, neuromuscular disease, non-invasive ventilation, obesity hypoventilation syndrome, respiratory failure.

INTRODUCTION

Over recent years, increasing numbers of patients with neuromuscular disease (NMD), chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome (OHS) and other forms of chronic respiratory failure are using non-invasive ventilation (NIV) for respiratory support.[1] Optimization of settings for NIV, including determination of fixed expiratory positive airway pressure (EPAP), requires time-consuming manual titration by experts. Guidelines recommend the use of attended polysomnography (PSG) as part of this process; however, these resources are not always available. Titration of ventilation based on bedside evaluation is commonly practiced but has been noted to decrease the quality of sleep and therefore is not ideal.[2] In addition, prescriptions based on the current condition only reflect requirements on that single visit. A patient's condition often changes over time due to disease progression, changes in body weight, alterations in prescribed medication, tissue oedema and variable posture.[3–5]

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Advances in technology demonstrate that NIV devices could meet changes in ventilation demand by automatically adjusting inspiratory pressure via the volume-assured pressure support (VAPS) algorithm. VAPS has already been examined for the treatment of chronic respiratory failure, OHS and NMD.[6–11] There is growing evidence that VAPS is as effective as manually titrated pressure support (PS) ventilation for treating respiratory insufficiency or failure.[6,10,12–15]

Some conditions that could be treated with VAPS may also have a component of upper airway obstruction; patients might therefore benefit from automatically adjusting EPAP (AutoEPAP). Such an AutoEPAP algorithm has recently been incorporated into the intelligent VAPS (iVAPS) mode to help maintain airway patency. A recent randomized clinical trial of the iVAPS AutoEPAP algorithm showed non-inferiority to fixed EPAP in patients with chronic hypoventilation,[16] predominantly in patients with OHS and COPD who are not ventilator-dependent.

The goal of this study was to compare the ability of the AutoEPAP algorithm to manage upper airway obstruction compared with manual EPAP in iVAPS mode in chronic respiratory failure patients receiving NIV. The hypothesis was that the automatic settings determined by the AutoEPAP algorithm would be non-inferior to manual EPAP in preventing desaturation. We also aimed to examine the effect on ventilation parameters, gas exchange and sleep quality.

METHODS

Study design

This prospective, multicentre, single-blind, randomized, crossover, non-inferiority trial was conducted at six sites in the United States. The study protocol was approved by the Western Institutional Review Board (IRB) and the IRB at each participating centre, and patients provided written informed consent before enrolment in the trial. The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Study oversight and monitoring were provided by the ResMed Medical Affairs Department (San Diego, CA, USA). The study was registered at clinicaltrials.gov (NCT02683772).

Patients

Eligible patients were adults with documented chronic respiratory failure. Sleep hypoventilation was defined as those with historical transcutaneous carbon dioxide ($TcCO_2$, increase of ≥10 mm Hg and/or daytime hypercapnia, defined as $PaCO_2$ > 45 mm Hg). In addition to hypoventilation, all subjects had previously documented sleep apnoea or an apnoea–hypopnoea index (AHI) ≥5/h from a diagnostic study or recorded from the patient's NIV device. The rationale for this criterion was to include subjects with a range of upper airway collapsibility, which might be reflected in a prior sleep apnoea diagnosis or otherwise with episodes of discreet respiratory events leading to an elevated AHI. Subjects had been using NIV in spontaneous-timed (ST) or VAPS mode for ≥3 months and had EPAP settings reviewed within the previous 12 months. Exclusion criteria included non-compliance with NIV (average usage of <4 h/night); use of oxygen therapy ≥5 L/min; acute disease exacerbation requiring hospitalization within the last 3 months; acute illness or medical instability; untreated non-OSA sleep disorders; surgery of the upper airway, nose, sinus or middle ear within the previous 90 days; and inability to provide informed consent and/or comply with the study protocol.

Procedures

All participants completed two overnight, in-laboratory PSG studies, one each using manual EPAP and AutoEPAP in iVAPS mode on NIV (Astral 150, ResMed Corp.), assigned in random order, usually on two consecutive nights. The subject was blinded to the intervention by shielding the display of the Astral ventilator. To perform titration, the titrating technician was aware of the intervention. All sites were instructed to set the NIV device in VAPS mode (iVAPS) as close to the patient's current NIV settings as possible. On the night that the patient was put on iVAPS with AutoEPAP, sites were instructed to keep the range 'open', so the algorithm could be tested across the full range (EPAP: 5–15 cm H_2O and PS: 4–20 cm H_2O). All sites and investigators were instructed to place each patient's clinical need and safety first. Therefore, clinically required NIV setting adjustments were permitted. On the manual EPAP night, technicians titrated the EPAP according to the American Academy of Sleep Medicine accredited laboratory standards, utilizing respiratory effort belts, snoring and desaturations in the absence of flow signals.[17] On each PSG night, $TcCO_2$ was measured using a bedside monitor (SenTec Digital Monitor, SenTec Inc Fenton, MO, USA). All PSG studies were scored by a registered polysomnographic sleep technologist without knowledge of the intervention according to the American Academy of Sleep Medicine criteria in a central core laboratory at the University of California, San Diego, USA. To assure blinding of the scoring laboratory, no data from the Astral ventilator, mask pressures or respiratory flow were recorded in the PSG software.

Outcomes

The primary outcome was the 4% oxygen desaturation index (ODI4%). Secondary objectives assessed whether the AutoEPAP algorithm was effective for treating respiratory failure and included the device-reported AHI, $TcCO_2$ and sleep parameters during use of NIV with AutoEPAP versus manual EPAP.

Sample size

The study was powered to demonstrate ODI4% non-inferiority between NIV with AutoEPAP versus manual EPAP based on a non-inferiority margin of 2. Sample size calculations assumed an expected mean difference in ODI4% of 0, with an SD of 1.55, power of 80% and two-sided alpha of 0.05. Power calculations based on a paired two-sided t-test showed that 23 patients would be sufficient. To allow for dropouts and to maximize study power, a decision was made to enrol up to 40 subjects.

Statistical analysis

All statistical analyses were generated using SAS version 9.3 (SAS Institute Inc. Cary, NC, USA) or later. All programming code was independently peer reviewed for accuracy. Heterogeneity of response across sites was tested using analysis of variance (ANOVA) based on a two-sided *P*-value of 0.15.

The intention-to-treat (ITT) population included all randomized patients who began the first study PSG night. The evaluable population included all patients from the ITT population who fulfilled the inclusion/exclusion criteria and completed study assessments as defined in the protocol. All primary and secondary endpoint analyses were performed on the evaluable population, while safety analyses included the ITT population.

Descriptive statistics were calculated for continuous variables, and frequencies and percentages were calculated for categorical data. Tests for normality were generated for continuous variables, as appropriate, and in addition, data were inspected for symmetry and severe outliers. For paired comparisons of continuous variables, the distribution of the data was considered, and in cases where the results were skewed, a Wilcoxon signed-rank or sign test was used, as appropriate. Otherwise, a paired t-test was utilized based on an alpha of 0.05.

The null (H_0) and alternative (H_1) hypotheses for the primary endpoint were based on a non-inferiority test using a non-inferiority margin (d) of 2 events/h, where $\mu A - B$ is the mean paired difference in ODI4% between AutoEPAP and manual EPAP:

$$H_0 : \mu A - B > d \text{ (AutoEPAP algorithm is inferior)}$$

$$H_1 : \mu A - B \leq d \text{ (AutoEPAP algorithm is non-inferior)}$$

The primary hypothesis was tested using a one-sided paired t-test of the difference, and the 95% upper one-sided confidence bound for the mean paired difference in ODI4% between manual and AutoEPAP was calculated. A crossover analysis was performed to investigate the influence of a possible period effect on the primary endpoint.

Subgroup analyses were performed on the primary endpoint based on disease type (COPD, NMD and OHS and other combined) and ventilator dependency (dependent vs non-dependent). An ANOVA was generated to compare differences in the primary endpoint between AutoEPAP and manual EPAP across subgroups.

RESULTS

Study population

Between April 2016 and July 2017, a total of 43 patients were enrolled and provided informed consent; 42 of these were randomized and met the inclusion/exclusion criteria. The trial was stopped after recruitment goals were met. Three patients were found to be ineligible after randomization, and one patient had a protocol violation. Therefore, 38 patients were included in the evaluable population (Fig. 1). The majority of patients were males (73.7%), and the most common primary

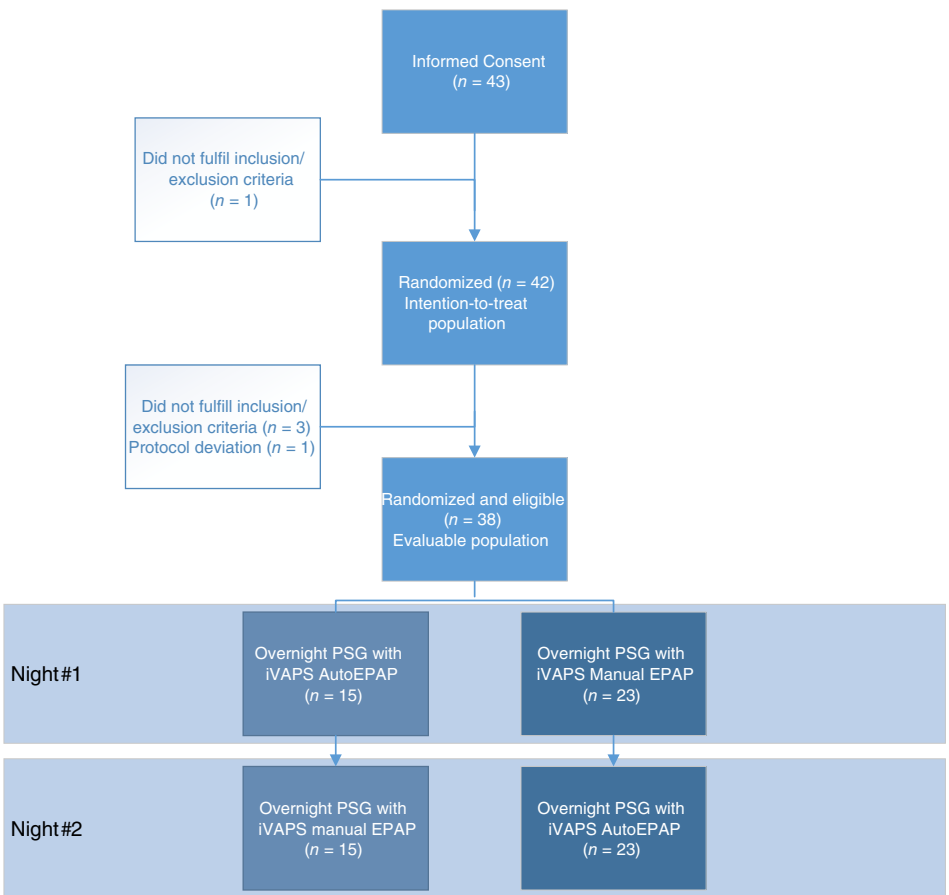

Figure 1 Study flow diagram. AutoEPAP, automatic expiratory positive airway pressure; iVAPS, intelligent volume-assured pressure support; PSG, polysomnography.

diagnosis was NMD (45%) (Table 1). Data regarding subject characteristics by study site and diagnosis are presented in Tables S1 and S2 (Supplementary Information). In the 24 patients with available data, AHI at enrolment was 30.9 ± 26.3/h (range: 5.3–105.8). NIV device settings were not significantly different between the two study nights (AutoEPAP and manual EPAP) (Table 2).

Table 1 Demographics, clinical characteristics and NIV settings at baseline

	Patients (n = 38)
Gender, *n* (%)	
Male	28 (73.7)
Female	10 (26.3)
Age (years)	
Mean ± SD (median)	55.33 ± 16.01 (58.53)
Minimum, maximum	18.0, 81.0
Race, *n* (%)	
Asian	1 (2.6)
Black/African American	8 (21.1)
Native Hawaiian or other Pacific Islander	1 (2.6)
White	23 (60.5)
Unknown/not available	5 (13.2)
Body mass index (kg/m^2)	
Mean ± SD (median)	31.41 ± 9.84 (30.12)
Minimum, maximum	15.0, 57.2
Primary diagnosis, *n* (%)	
Chronic obstructive pulmonary disease	11 (28.9)
Neuromuscular disease	17 (44.7)
Obesity hypoventilation syndrome	4 (10.5)
Other	6 (15.8)
Apnoea–hypopnoea index (events/h)	
Mean ± SD (median)	30.91 ± 26.29 (17.80)
Minimum, maximum	5.3, 105.8 (24)
Ventilator dependent, *n* (%)	
No	31 (81.6)
Yes	7 (18.4)
Device mode at enrolment, *n* (%)	
Bi-level ST	12 (31.6)
VAPS	26 (68.4)
Device settings at enrolment	
IPAP (cm H_2O)	
Mean ± SD (median)	16.8 ± 4.7 (17.0)
Minimum, maximum (n)	6, 29 (29)
EPAP (cm H_2O)	
Mean ± SD (median)	7.4 ± 3.4 (6.0)
Minimum, maximum (n)	4, 16 (37)
Back-up rate (breaths per min)	
Mean ± SD (median)	8.74 ± 6.22 (12.00)
Minimum, maximum (n)	0.0, 18.0 (38)
Duration of NIV treatment (years)	
Mean ± SD (median)	3.16 ± 3.75 (1.66)
Minimum, maximum	0.2, 17.0

EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; ST, spontaneous-timed; VAPS, volume-assured pressure support.

Primary endpoint

Mean ODI4% was lower during NIV with AutoEPAP versus manual EPAP (Table 3, Fig. 2).Treatment order had no effect on the results (P = 0.35), and data were homogeneous across study sites (Kruskal–Wallis P-value <0.15). AutoEPAP was statistically non-inferior using the proposed one-sided paired t-test using a significance level of 0.05 and a non-inferiority margin of 2 events/h (P = 0.01). However, testing showed that the data had a non-normal distribution (Shapiro–Wilk test, P < 0.0001). A non-parametric test (Wilcoxon signed rank) highlighted the non-inferiority of AutoEPAP compared with manual EPAP (P < 0.0001) (Table 3). The mean difference in ODI4% between AutoEPAP and manual EPAP was not significantly different between subgroups based on disease type (i.e. neuromuscular, COPD or OHS and other combined) (Fig. 2) (P = 0.49) or ventilator dependency status (P = 0.34).

Secondary endpoints

Settings for iVAPS mode and resulting device output on the two PSG study nights are shown in Table 2. Mean EPAP and inspiratory positive airway pressure (IPAP) were higher during AutoEPAP, but ventilation and mean rapid shallow breathing index (a marker of work of breathing) were similar on both nights. Mean oxygen saturation and $TcCO_2$ were similar with the two NIV modes (Table 4). On average, patients spent significantly less time in Stage N1 sleep, more time in rapid eye movement (REM) sleep and had significantly fewer arousals during AutoEPAP versus manual EPAP (Table 4). Data for subgroups of neuromuscular, COPD and OHS or other subjects are reported in Tables S3–S5 (Supplementary Information). Data for ventilator dependent and non-dependent subgroups are reported in Tables S6 and S7 (Supplementary Information).

Adverse events

No serious adverse events were reported during the study. One non-serious adverse event (asthma exacerbation) occurred during the second PSG night (manual EPAP) in one patient, which resolved after utilization of routine treatment. This was determined by the site investigator to be not related to the device or device mode.

DISCUSSION

In the therapy of obstructive sleep apnoea, automatic EPAP algorithms have long been shown to be effective in assessing and treating upper airway obstruction. Many patients have complicated issues with sleep-disordered breathing because they have both chronic hypoventilation as well as abnormalities in upper airway collapsibility. As both factors need to be addressed, the goal of this investigation was to evaluate the ability of an automatic EPAP algorithm in VAPS mode to control upper airway obstruction while remaining effective at treating hypoventilation, without requiring titration by a sleep laboratory technician.

Table 2 Non-invasive ventilation device settings and reported pressures during study nights

	Mean ± SD (median) Minimum, maximum (*n*)		
	iVAPS AutoEPAP (*n* = 38)	iVAPS manual EPAP (*n* = 38)	*P*-value
iVAPS settings			
EPAP setting (cm H_2O)	N/A	7.6 ± 3.5 (6.5) 4, 16 (38)	N/A
Minimum EPAP setting (cm H_2O)	6.3 ± 2.5 (5.0) 4, 15 (37)	N/A	N/A
Maximum EPAP setting (cm H_2O)	15.0 ± 1.3 (15.0) 9, 20 (37)	N/A	N/A
Minimum PS (cm H_2O)	3.2 ± 1.2 (4.0) 2, 6 (37)	3.1 ± 1.2 (3.0) 2, 6 (38)	0.57
Maximum PS (cm H_2O)	19.4 ± 2.0 (20.0) 10, 20 (37)	19.3 ± 2.2 (20.0) 10, 22 (38)	0.53
Target Va (L/min)	6.03 ± 2.31 (5.20) 3.6, 16.7 (37)	6.01 ± 2.32 (5.20) 3.5, 16.7 (38)	0.32
iVAPS report parameters			
EPAP median (cm H_2O)	10.24 ± 3.02 (10.50) 4.2, 14.8 (36)	7.04 ± 3.28 (5.80) 3.8, 15.6 (37)	0.0002
EPAP 95% (cm H_2O)	13.30 ± 2.30 (14.20) 6.4, 16.0 (36)	7.42 ± 3.29 (6.40) 4.0, 16.0 (37)	<0.0001
IPAP median (cm H_2O)	19.82 ± 6.11 (18.00) 11.0, 34.8 (36)	17.43 ± 5.26 (16.60) 7.8, 28.0 (37)	0.0003
IPAP 95% (cm H_2O)	25.93 ± 6.55 (24.00) 16.2, 35.6 (36)	23.06 ± 5.06 (23.80) 12.4, 32.0 (37)	0.0001
Vt median (L)	0.486 ± 0.131 (0.456) 0.35, 1.00 (36)	0.460 ± 0.131 (0.432) 0.27, 1.00 (37)	0.06
Vt 95% (L)	0.744 ± 0.160 (0.744) 0.43, 1.00 (36)	0.698 ± 0.198 (0.702) 0.11, 1.00 (37)	0.18
RR median (BPM)	16.8 ± 3.3 (16.0) 12, 26 (36)	17.3 ± 3.7 (17.0) 12, 27 (37)	0.35
RR 95% (BPM)	21.9 ± 4.5 (21.0) 15, 32 (36)	21.5 ± 5.3 (20.0) 14, 38 (37)	0.78
RSBI	37.02 ± 12.27 (36.05) 16.0, 66.7 (36)	40.94 ± 16.04 (36.82) 16.0, 81.5 (37)	0.13

Values are mean ± SD (median), with minimum, maximum values (*n*) below. *P*-values generated from a paired t-test or sign test, as appropriate.

AutoEPAP, automatically adjusting EPAP; BPM, breaths per minute; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; iVAPS, intelligent volume-assured PS; N/A, not applicable; PS, pressure support; RR, respiratory rate; Va, alveolar ventilation; Vt, tidal volume.

Table 3 ODI4% during non-invasive ventilation with automatic versus manual expiratory positive airway pressure (n = 38)

	AutoEPAP	Manual EPAP	Paired difference	95% Upper one-sided confidence bound	*P*-value
ODI4% (/h)	3.16 ± 5.67	7.61 ± 18.87	−4.45 ± 17.23 (−96.7, 10.1)	0.27	0.0134[†] <0.0001[‡]

Values are mean ± SD (range), unless otherwise stated.

[†]One-sided paired t-test.

[‡]Wilcoxon signed-rank test.

AutoEPAP, automatically adjusting EPAP; EPAP, expiratory positive airway pressure; ODI4%, 4% oxygen desaturation index.

The results of this study showed that AutoEPAP was non-inferior to manual EPAP for improving ODI4%, as a measure of upper airway obstruction, in patients with respiratory failure secondary to a variety of underlying hypoventilation disorders. The mean difference between AutoEPAP and manual EPAP in normalizing ODI4% was similar across disease types and ventilator dependency.

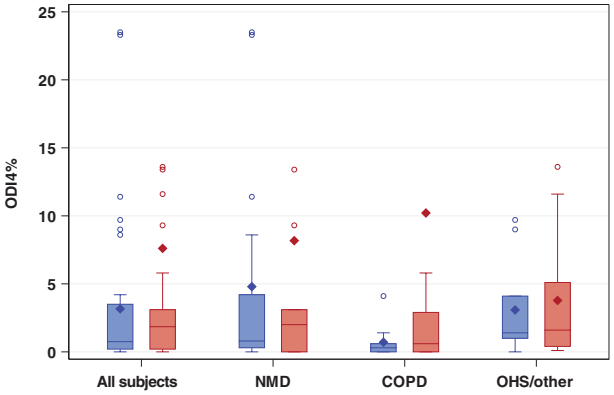

Figure 2 Difference in 4% oxygen desaturation index (ODI4%) between automatically adjusting expiratory positive airway pressure (AutoEPAP) (■) and manual EPAP (■) in all subjects, and subjects grouped by aetiology of respiratory failure. Obesity hypoventilation syndrome (OHS) and other binned together due to small sample size. ODI4% while using AutoEPAP was non-inferior to manual EPAP in all subjects. There were no significant differences in ODI4% across the subgroups of neuromuscular disease, chronic obstructive pulmonary disease (COPD) and OHS and other combined. Three outliers not displayed where ODI4% > 40.

AutoEPAP resulted in higher delivered mean EPAP levels than those set under manual EPAP. While higher EPAP might improve upper airway resistance and potentially facilitate triggering, one concern might be a negative effect on ventilation, work of breathing or sleep quality. However, we did not observe any statistically significant difference in modes with respect to ventilation parameters, or gas exchange, suggesting that AutoEPAP did not impair respiratory mechanics, and PS was appropriately maintained by the iVAPS algorithm. In addition, parameters reflecting sleep quality were improved, including decreased arousals and increased REM sleep.

We utilized ODI4% as the primary outcome rather than AHI as AHI determined by the device would not meet current standards for classifying hypopnoeas and would be utilizing the same algorithms being used to auto-titrate the EPAP level. Moreover, transient hypoventilation may be seen in this population, which may be mistaken for upper airway obstructive events when relying solely on flow signals. The effectiveness of AutoEPAP on ODI4% without worsening ventilation suggests that the algorithm is able to appropriately classify events as obstructive; if events were due to hypoventilation, they might have persisted or even worsened at higher EPAP levels. The ODI4% findings were similar to those observed in the device-measured residual respiratory event index, which were similar between AutoEPAP and manual titration.

The results of our study show an outcome similar to a recent investigation of AutoEPAP in patients with both chronic hypoventilation and upper airway obstruction.[16] However, there were some differences between the studies. We evaluated both ventilation-dependent and non-dependent patients using a home ventilator, versus non-dependent patients using a bi-level device in the previous study. In addition, NMD was predominant in our study, whereas OHS was most common in the prior study. The studies also had different primary endpoints—ODI4% in our case and AHI in the previous study. Given the differences between the studies in terms of primary outcome measures and underlying diseases, their combined results provide growing evidence of the efficacy of AutoEPAP.

Auto-titrating NIV may have benefits with respect to sleep quality. A prior study of auto-titrating PS reported less percent stage N1 sleep and fewer arousals compared to standard NIV.[13] Similarly, patients in our study spent significantly less time in stage N1 sleep with AutoEPAP versus manual EPAP, and the mean number of arousals was significantly lower. This finding could indicate easier sleep initiation and a trend towards a longer period of deep sleep during use of automatic versus manual settings.[13] Patients receiving home-based NIV have reported more restful sleep when using iVAPS compared with conventional high-intensity NIV, although objective sleep quality parameters were not significantly different.[6] It is possible that trends towards improved sleep during iVAPS could be enhanced when iVAPS is used with AutoEPAP versus manual EPAP, but this remains to be determined in future studies.

Adherence to therapy is another important factor to consider during long-term use of NIV. In one study, iVAPS led to one additional hour per night of use compared with standard PS.[14] Such improvements in adherence could have an impact on patient outcomes,[18] and therefore, future studies are warranted on whether the addition of AutoEPAP further improves use.

Strengths of this study include its randomized design, multicentre performance, centralized and blinded scoring of sleep studies, experienced clinicians/investigators and the inclusion of a heterogeneous population reflective of a clinical population. However, there were a number of limitations. The two NIV modes were only compared over a single night of therapy. Therefore, comparative longer term effects of the AutoEPAP mode need to be investigated, including effectiveness and compliance, particularly given the higher EPAP pressures observed with AutoEPAP. We studied patients already using NIV, in whom previous EPAP settings were available. While this primarily had the effect of minimizing the need for manual titration, we cannot generalize our findings to an NIV-naïve group. We did not collect detailed lung function or blood gas information and instead relied on the referring clinician diagnosis and patient history. Most patients had been on NIV for years, and collecting contemporary data would have been difficult but, nonetheless, may have provided additional information. The study cohort had few women, who may benefit from different AutoEPAP algorithms from men.[19] Finally, we cannot draw specific non-inferiority conclusions for each group as our numbers in each group were relatively small, and this would require a dedicated study for each group rather than our approach of showing overall non-inferiority.

In conclusion, a single night of NIV using iVAPS with AutoEPAP was non-inferior to iVAPS with manual EPAP with respect to mean ODI4% in a group of patients with respiratory failure secondary to NMD, COPD, OHS and other causes. There was no suggestion

Table 4 Sleep parameters

	Mean ± SD (median) Minimum, maximum(*n*)		
	iVAPS AutoEPAP (*n* = 38)	iVAPS manual EPAP (*n* = 38)	*P*-value
Sleep parameters			
TST (min)	303.3 ± 79.58 (315.8) 55.9, 410.5 (38)	308.0 ± 82.37 (328.3) 47.5, 450.5 (38)	0.75
Stage N1 (% of TST)	16.18 ± 11.50 (12.90) 1.9, 54.6 (38)	20.47 ± 14.69 (17.10) 1.4, 73.1 (38)	0.01
Stage N2 (% of TST)	50.03 ± 13.83 (51.35) 11.9, 72.9 (38)	48.52 ± 17.20 (48.65) 6.5, 76.6 (38)	0.55
Stage N3 (% of TST)	17.93 ± 17.98 (11.30) 0.0, 77.3 (38)	17.74 ± 18.36 (14.45) 0.0, 74.8 (38)	0.61
REM sleep (% of TST)	15.58 ± 8.54 (16.05) 0.0, 32.1 (38)	12.76 ± 7.44 (12.80) 0.0, 26.3 (38)	0.04
Arousals (/h)	25.85 ± 17.39 (20.70) 2.9, 87.0 (38)	31.91 ± 20.19 (24.70) 3.6, 87.2 (38)	0.04
Sleep efficiency (%)	73.70 ± 16.41 (73.95) 25.6, 94.1 (38)	73.89 ± 19.05 (76.47) 11.1, 98.1 (38)	0.95
Device data			
AHIflow (/h)	4.71 ± 5.55 (2.10) 0.2, 21.4 (36)	7.84 ± 15.39 (3.80) 0.0, 91.2 (37)	0.22
Mean SpO_2 (%)	94.24 ± 2.36 (94.00) 88.0, 99.0 (34)	94.53 ± 2.78 (95.00) 88.0, 99.0 (36)	0.81
Median SpO_2 (%)	94.53 ± 2.36 (95.00) 89.0, 99.0 (34)	94.86 ± 2.66 (95.00) 89.0, 99.0 (36)	0.69
Mean PCO_2 (mm Hg)	45.49 ± 6.62 (47.00) 33.2, 62.7 (35)	45.38 ± 7.17 (44.80) 33.2, 65.2 (36)	0.83
Median PCO_2 (mm Hg)	45.67 ± 6.62 (48.10) 33.2, 63.0 (35)	45.27 ± 7.13 (44.75) 32.9, 65.7 (36)	0.44

Values are mean ± SD (median), with minimum, maximum values (*n*) below. *P*-values generated from a paired t-test or sign test, as appropriate.

AHIflow, apnoea–hypopnoea index based on device flow signal; AutoEPAP, automatically adjusting expiratory positive airway pressure; iVAPS, intelligent volume-assured pressure support; PCO_2, carbon dioxide pressure; REM, rapid eye movement; SpO_2, oxygen saturation; TST, total sleep time.

of compromise in ventilation, and sleep parameters improved while using AutoEPAP. Additional research is needed to compare these modes over longer treatment durations and to evaluate the use of AutoEPAP iVAPS in NIV-naïve patients.

Data availability statement: Data from this study will not be shared to the public. Additional study information can be requested from the corresponding author.

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Abbreviations: AHI, apnoea–hypopnoea index; ANOVA, analysis of variance; AutoEPAP, automatically adjusting EPAP; BPM, breaths per minute; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; IRB, Institutional Review Board; iVAPS, intelligent VAPS; ITT, intention-to-treat; NIV, non-invasive ventilation; NMD, neuromuscular disease; ODI4%, 4% oxygen desaturation index; OHS, obesity hypoventilation syndrome; PCO_2, carbon dioxide pressure; PS, pressure support; PSG, polysomnography; REM, rapid eye movement; RR, respiratory rate; SpO_2, oxygen saturation; $TcCO_2$, transcutaneous carbon dioxide; TST, total sleep time; VAPS, volume-assured PS; Vt, tidal volume.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Table S1 Subject demographics stratified by study site.
Table S2 Subject demographics by primary diagnosis.
Table S3 Selected parameters from neuromuscular subgroup.
Table S4 Selected parameters from COPD subgroup.
Table S5 Selected parameters from OHS and other subgroup.
Table S6 Selected parameters from non-dependent subgroup.
Table S7 Selected parameters from dependent subgroup.

Visual Abstract Intelligent Volume-Assured Pressure Support (iVAPS) with AutoEPAP algorithm controls upper airway obstruction in chronic respiratory failure.

