**Supplementary materials for:**

**Treating chronic hypoventilation with automatic adjustable versus fixed EPAP intelligent volume-assured positive airway pressure support (iVAPS); a randomized controlled trial**

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**ResMed Ltd, iVPAPs device algorithms**

iVAPS is servo-controlled ventilator that is designed to maintain preset target alveolar minute ventilation by monitoring delivered ventilation and adjusting the pressure support appropriately. The target alveolar ventilation can be set according to clinician judgement or determined by a ‘learn target’ procedure, according to measurements appropriate to the individual (see below). A fixed back up rate is not used, instead the back-up rate is two thirds of the preset target rate during spontaneous ventilation (i.e., it remains ‘in the background’ to give the patient the maximum opportunity to trigger spontaneously) and automatically shifts to the set target rate during sustained apnea. The autoEPAP mode uses an algorithm that responds to apnea and flow limitation to correct upper airway obstruction by increasing EPAP. Apnea is considered to occur when alveolar ventilation has decreased to less than 5% of the target ventilation and flow limitation is determined by flow shapes indicative of upper airway obstruction. The algorithm does not increase EPAP in the presence of central apnea.

**METHODS**

**Inclusion Criteria**

* Ability to provide written informed consent
* Age ≥18 years
* Documented diagnosis of COPD, OHS or NMD with sleep hypoventilation (historical PtCO2 increase ≥10 mmHg) and/or daytime hypercapnia (>45 mmHg)
* Current use of non-invasive ventilation for ≥3 months
* AHI ≥5/h (as documented in diagnostic or pressure determination sleep study report)

**Exclusion Criteria**

* Not compliant on NIV (i.e. usage <4 h/night)
* Severe asthma
* Pregnancy
* Use of oxygen therapy (i.e. >4 L/min)
* Tracheostomy
* Acute illness, medical complications or medically unstable
* PAP therapy contraindicated
* Surgery of the upper airway, nose, sinus, or middle ear within the previous 90 days
* Untreated, non-OSA sleep disorders, including but not limited to; insomnia, periodic limb movement syndrome, or restless legs syndrome
* Requirement for ventilatory support during wakefulness
* Pre-existing conditions: severe bullous lung disease, recurrent pneumothorax or pneumomediastinum, low blood pressure, cerebrospinal fluid leak, recent cranial surgery or trauma.
* Severe developmental delay and unable to follow tasks as instructed in the protocol
* Considered by the investigator as unsuitable for inclusion:
* no comprehension of English
* Unable or unwilling to provide written informed consent
* Physically unable to comply with the protocol
* Unsuitable to participate in the trial for any other reason

**Learn Target procedure**

Height was measured using a stadiometer (height is used by the device to estimate anatomical deadspace). A target alveolar ventilation and target respiratory rate were determined by the iVAPS ‘Learn Targets’ procedure, with the iVAPs device set at the patient’s usual EPAP and minimum and maximum PS at the manufacturer’s default settings. During the ‘Learn Targets’ procedure, the research assistant instructed the patient to remain awake and breath on the iVAPS ventilator circuit in a relaxed manner while being monitored for 20 minutes during which time the device delivered EPAP and PS (taken from minimum PS) without backup breaths (like spontaneous [S] mode). The ‘Learn Targets’ period is split into two windows. During the first window of 15 minutes, no calculations are made. For the last window of 5 minutes, tidal volume and respiratory rate for individual breaths are stored from which the target alveolar ventilation and target breath rate are calculated using median breath rate, median tidal volume and the anatomical deadspace estimated from the patient height setting.

**Arteriolized capillary blood gas measurements**

Arteriolized capillary blood gases were performed on room air on all but the two patients (COPD and NMD) who required daytime supplemental oxygen. The sample was taken during work hours (9am-5 pm), i.e., during the initial assessment appointment (after study consent). The blood gas was done during the initial assessment to ensure that patients were clinically stable prior to overnight testing with the study device. The test was performed with the patient in the sitting position.

**Re-titration night initial device settings**

All patients with home S/T mode devices had duty cycles prescribed using fixed inspiratory:expiratory (I:E) ratios, however the study device uses a duty cycle window, delimited by minimum and maximum inspiratory times (Ti min and Ti max) appropriate to the patient’s ‘Learn Target’ respiratory rate. To ensure consistency, the initial Ti min and Ti max parameters were set using a standard rule for COPD (Ti cycle: 30-40%) and non-COPD (Ti cycle: 30-50%) participants. Specifically, for non-COPD patients the optimal limits of Ti are likely to be equally spread (up to 10% above or 10% below) around a Ti that corresponds to duty cycle of 0.40. Hence, we used a Ti min corresponding to duty cycle of 0.3 and a Ti max corresponding to a duty cycle of 0.5. For COPD, a bias towards a shorter duty cycle of 0.35 is appropriate. Hence, for COPD a Ti min (0.30) and max (0.40) that corresponds to an appropriate spread (5% above or 5% below) around a duty cycle of 0.35 was used to ensure adequate time for exhalation in these patients. Because some patients were receiving spontaneous mode PS at home and for consistency in the study, all patients were prescribed an initial back up rate 20% less than their ‘Learn Target’ spontaneous breath rate. Some patients had older NIV PS devices which did not specify some settings, e.g., cycle timing and so initial ‘trigger’ and ‘cycle’ were set on the manufacturer default of ‘medium’ and the initial rise time setting was 150msec for all patients. We alerted the overnight titration scientists when the non-pressure settings established for home therapy were different to re-titration night default initial settings (see above) to ensure any needed adjustments would occur early during the night.

**Changes made and protocol violations**

One software change was made during the trial related to the ‘device ramp period’. Ramping of pressure occurs at the start of treatment when the pressure rises from the minimum set pressure to the therapeutic pressure. The device ramp is a comfort feature to assist sleep onset and does not have safety consequences. Early in the trial it was noted that the AutoEPAP was detecting and responding to accumulated flow limitation during the Ramp period. For this reason, a software change was made which corrected this problem. This issue affected 3 patients (4 sleep studies) and, with approval of the local ethics committee, these patients were asked if they would repeat their PSG studies – all agreed and there were no changes to the randomization order. To facilitate achieving the required subject numbers, 2 patients were recruited who met all inclusion criteria, except the diagnosis did not match the specified disease categories. They had similar underlying physiology to the other conditions being studied. One patient had chronic airflow limitation, due to cystic fibrosis rather than COPD. He was 54 years of age with very severe airflow limitation (FEV1=0.72L, 18% of predicted, FEV1/FVC=0.72/1.68, 55% of predicted) and moderately severe OSA (AHI= 17/hr) who had developed CO2 retention (PCO2=66mm Hg) during an exacerbation and was established on NIV treatment. The other patient was a 65-year-old man with severe congenital scoliosis (confirmed on thoracic CT scan) and an associated severe restrictive defect (FVC=1.37L, 37% of predicted, FEV1/FVC=0.99/1.37=0.72, 96% of predicted). He had severe OSA (AHI=39.4/hour) and developed CO2 retention (PCO2=57mmHg) after 11 years of CPAP treatment and so had been transferred to NIV.

**Table S1.** FixedEPAP iVAPS and AutoEPAP iVAPS setting guidelines for device parameters

|  |  |  |
| --- | --- | --- |
| **Parameter** | **FixedEPAP iVAPS** | **AutoEPAP iVAPS** |
| EPAP (cmH2O) | As per optimum EPAP setting seen in ST mode  (i.e. Visit 2, ST mode titration study) | n/a |
| Min EPAP (cmH2O) | n/a | Based on disease state:  COPD: 5.0 cmH2O1 OHS: 8.5 cmH2O2 NMD: 4.0 cmH2O3 |
| Max EPAP (cmH2O) | n/a | Recommended: Default setting  (15 cmH2O) (Alternative: Clinician’s discretion\*) |
| Min PS (cmH2O) | Recommended: Default setting  (2 cmH2O) (Alternative: Clinician’s discretion\*) | Recommended: Default setting  (2 cmH2O) (Alternative: Clinician’s discretion\*) |
| Max PS (cmH2O) | Recommended: Default setting  (15 cmH2O) (Alternative: Clinician’s discretion\*) | Recommended: Default setting  (15 cmH2O) (Alternative: Clinician’s discretion\*) |
| Patient height/ arm span (cm) | As measured by clinician | As measured by clinician |
| Learn Target – for Target patient rate & Target Va | Perform Learn Target procedure as detailed in Clinical manual  (see attachments) | Perform Learn Target procedure as detailed in Clinical manual  (see attachments) |
| Ti min | Recommended: Default setting (0.3 sec) (Alternative: Clinician’s discretion\*) | Recommended: Default setting (0.3 sec) (Alternative: Clinician’s discretion\*) |
| Ti max | Recommended: Default setting (2.0 sec) (Alternative: Clinician’s discretion\*) | Recommended: Default setting (2.0 sec) (Alternative: Clinician’s discretion\*) |
| Rise Time | Recommended: Default setting  (300 msec) (Alternative: Clinician’s discretion\*) | Recommended: Default setting  (300 msec) (Alternative: Clinician’s discretion\*) |
| Trigger | Recommended: Default setting (Med) (Alternative: Clinician’s discretion\*) | Recommended: Default setting (Med) (Alternative: Clinician’s discretion\*) |
| Cycle | Recommended: Default setting (Med) (Alternative: Clinician’s discretion\*) | Recommended: Default setting (Med) (Alternative: Clinician’s discretion\*) |
| Ramp | Participant’s normal ramp | Participant’s normal ramp |
| Oxygen concentration | ≤4 L/min\*\* | ≤4 L/min\*\* |
| Humidification setting | At patient/clinician’s discretion | At patient/clinician’s discretion |
| Circuit settings | ‘AB filter’: ‘yes’ Mask type: Clinician’s discretion\* Tubing type: In accordance with tubing used | ‘AB filter’: ‘yes’ Mask type: Clinician’s discretion\* Tubing type: In accordance with tubing used |

COPD, chronic obstructive pulmonary disease; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; iVAPS, intelligent volume-assured pressure support; NMD, neuromuscular disorders; OHS, obesity hypoventilation syndrome; PS, pressure support; Ti, inspiratory time; Va, alveolar ventilation.

\*Clinician’s discretion = the investigator may change the setting if it is clinically appropriate and the default setting does not meet the clinical needs of the participant.

\*\* iVAPS is only compatible with oxygen ≤4L/min

1Based on mean EPAP value from: Kohnlein T, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicenter, randomized, controlled clinical trial. *Lancet Respir Med*. 2014;2:698-705.

2Janssens JP, Metzger M, Sforza E. Impact of volume targeting on efficacy of bi-level non-invasive ventilation and sleep in obesity-hypoventilation. *Resp Med*. 2009; 103:165-172.

3Bourke SC, *et al*. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol.* 2006; 5:140-147.

**RESULTS**

**Figure S1.** Comparison between AutoEPAP 95th centile pressure and FixedEPAP pressure on the respective study nights: individual data, medians (dots) and interquartile ranges

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**Table S2.** Post-hoc analyses, comparisons between re-titration night and iVAPS nights: PSG sleep breathing outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **S/T mode titration (n=25)** | **FixedEPAP (n=25)** | **P-value**  **(ST vs fixed)** | **AutoEPAP (n=25)** | **P-value**  **(ST vs auto)** |
| AHI, /h | 1.9 (0.4–3.6) | 2.4 (0.2–6.0) | 0.38 | 2.7 (1.7–6.5) | 0.12 |
| ODI3%, /h | 4.7 (0.8–10.0) | 3.5 (1.4–9.6) | 0.39 | 4.2 (2.5–11.0) | 0.62 |
| ODI4%, /h | 1.5 (0.4–4.2) | 1.1 (0.2–4.6) | 0.49 | 1.6 (0.1–5.9) | 0.93 |
| Oxygen saturation, % | 93.7±2.3 | 94.1±2.2 | 0.21 | 93.8±2.2 | 0.92 |
| Time with oxygen saturation <90%, min | 2.0 (0.1–27.2) | 0.4 (0–5.7) | 0.08 | 0.5 (0–22.0) | 0.78 |
| Lowest oxygen saturation, % | 85.2±5.8 | 88.0±2.8 | 0.18 | 86.5±4.7 | 0.22 |
| TcCO2 mean, mmHg\* | 45.5±6.5 | 46.8±6.1 | 0.32 | 47.4±5.0 | 0.19 |
| TcCO2 highest, mmHg | 52.1±11.4 | 52.8±8.2 | 0.78 | 53.2±5.4 | 0.74 |

\*n=24, due to Sen Tec device malfunction on one study night

Data are presented as median (interquartile range) or mean ± standard deviation.

AHI, apnea-hypopnea index; EPAP, expiratory positive airway pressure; N/A, not applicable; iVAPS, intelligent volume-assured positive airway pressure support; ODI3%, oxygen desaturation index 3%, ODI4%, oxygen desaturation index 4%; SpO2, oxygen saturation; TcCO2, transcutaneous carbon dioxide tension.

**Table S3.** Post-hoc analyses, comparisons between re-titration night and iVAPS nights: PSG sleep architecture outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **S/T mode titration (n=25)** | **FixedEPAP (n=25)** | **P-value (S/T vs fixed)** | **AutoEPAP (n=25)** | **P value S/T vs auto)** |
| Total recording time, min | 521.3±56.4 | 513.6±84.8 | 0.56 | 500.9±105.4 | 0.33 |
| Total sleep time, min | 333.9±86.2 | 340.7±110.9 | 0.69 | 331.4±109.3 | 0.92 |
| Sleep efficiency, % | 63.9±14.7 | 65.5±17.8 | 0.55 | 65.1±15.1 | 0.71 |
| Supine sleep, % | 44.7±36.4 | 51.9±36.4 | 0.27 | 50.1±34.0 | 0.48 |
| Sleep latency, min | 16.5 (10.2–32.8) | 16.5 (7.8–38.8) | 0.83 | 16.5 (9.2–35.0) | 0.88 |
| Stage 1, % | 24.2±12.7 | 26.2±14.2 | 0.48 | 24.1±13.0 | 0.96 |
| Stage 2, % | 54.9±11.0 | 50.6±12.4 | 0.08 | 52.3±12.3 | 0.25 |
| Stage 3, % | 8.2±7.1 | 89.0±7.1 | 0.46 | 10.1±7.4 | 0.18 |
| Stage REM, % | 12.6±6.3 | 14.2±9.4 | 0.36 | 13.5±5.4 | 0.44 |
| Respiratory arousal index, /h | 3.0 (1.0-6.6) | 3.3 (1.0–3.3) | 0.59 | 6.3 (2.4–8.9) | 0.10 |
| Spontaneous arousal index, /h | 28.4 (18.8–39.3) | 28.2 (16.7–41.8) | 0.92 | 24.5 (17.2–32.8) | 0.46 |
| Total arousal index, /h | 32.9 (21.6–49.7) | 31.2 (23.9–61.4) | 0.49 | 34.1 (18.8–42.0) | 0.92 |
| PLM index, /h | 0 (0–16.2) | 0 (0–38.0) | 0.11 | 1.9 (0–16.8) | 0.33 |

Data are presented as median (interquartile range) or mean ± standard deviation.

EPAP, expiratory positive airway pressure; iVAPS, intelligent volume-assured positive airway pressure support; N/A, not applicable; PLM, periodic leg movements; REM, rapid eye movement.

**Post-hoc analyses: Predictors of PSG sleep breathing outcomes**

Predictors of inter-individual differences between the treatment modes in sleep breathing outcomes were identified by linear regression, with significant univariate variables entered into a stepwise multivariate model with probability to enter of F ≤0.05, probability to remove of F ≥0.10.

Dependent variables were: difference (Auto – Fixed) in AHI, ODI (3% and 4%); minutes with oxygen saturation <90%, mean oxygen saturation, mean transcutaneous CO2, highest transcutaneous CO2.

Explanatory variables were: age; gender; body mass index; hypoventilation group (dichotomized dummy variables); difference (Auto – Fixed) in mean EPAP, IPAP,PS and median and 95th centile leak.

*Results of univariate and multivariate analyses*

*Difference (Auto–FixedEPAP) in* AHI

No predictors.

*Difference (Auto–FixedEPAP) in* ODI3%

Univariate predictor – difference in mean EPAP, r=–0.418, adjusted r2=0.139; p=0.038.

*Difference (Auto–FixedEPAP) in* ODI4%

Univariate predictors are shown in Table S4.

**Table S4.** Univariate predictors of EPAP and leak

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictors** | **r** | **Adjusted r2** | **P-value** |
| Difference in mean EPAP, cmH2O | –0.455 | 0.173 | 0.022 |
| Difference in 95th centile leak, L/min | –0.430 | 0.150 | 0.032 |

Multivariate predictors: Difference in mean EPAP and difference in 95th centile leak, r =0.585, adjusted r2=0.282, p=0.010

*Difference (Auto–FixedEPAP) in minutes saturation <90%*

Univariate predictors are shown in eTable5.

**Table S5.** Univariate predictors of difference in minutes with oxygen saturation <90%

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictors** | **r** | **Adjusted r2** | **P-value** |
| Difference in median leak, L/min | 0.48 | 0.234 | 0.014 |
| Difference in mean EPAP, cmH2O | –0.46 | 0.18 | 0.020 |
| Difference in mean IPAP, cmH2O | –0.443 | 0.16 | 0.026 |
| Gender, male | 0.42 | 0.144 | 0.035 |

Multivariate predictors: difference in median leak and difference in mean EPAP, r=–0.622; adjusted r2=0.33, p=0.005.

*Difference (Auto–FixedEPAP) in mean oxygen saturation*

Univariate predictor: difference in mean EPAP, r=0.47, adj r2=0.19; p= 0.017.

*Difference (Auto–FixedEPAP) in mean transcutaneous CO2*

Univariate predictors are shown in e-Table 5.

**Table S6.** Univariate predictors of difference in mean transcutaneous CO2 (mm Hg)

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictors** | **r** | **Adjusted r2** | **P-value** |
| Difference in mean EPAP, cmH2O | –0.43 | 0.147 | 0.036 |
| COPD vs non-COPD | –0.43 | 0.146 | 0.037 |
| Increasing age, years | –0.41 | 0.132 | 0.046 |

Multivariate predictor: difference in mean EPAP, r=–0.43, adjusted r2=0.147; p=0.036.

*Difference (Auto-FixedEPAP) in highest Transcutaneous CO2*

Univariate predictor: COPD vs non-COPD group: r=–0.421, adjusted r2=0.14; p=0.04.

**SUMMARY**

There were no predictors of the difference in AHI. The difference in mean EPAP was the only predictor of difference in ODI3% (r=–0.418, adjusted r2=0.139; p=0.038) and mean oxygen saturation (r=0.47, adjusted r2=0.19; p=0.017) between the 2 modes. The difference in mean EPAP was an independent predictor, along with 95th centile leak of ODI4% (0.585, adjusted r2=0.282, p=0.010). Univariate predictors of the difference between modes of time with oxygen saturation<90% were the difference in median leak, difference in mean EPAP, the difference in mean IPAP and male gender. The difference in median leak and mean EPAP were significant in multivariate analysis (r=–0.622, adjusted r2=0.331; p=0.005). The only predictor of the difference in highest TcCO2 was COPD vs non-COPD group (p=0.04). Univariate predictors of the difference in mean TcCO2 were difference in mean EPAP, COPD vs non-COPD group, and age; only the difference in mean EPAP was significant in multivariate analysis (r=–0.43, adjusted r2=0.147; p=0.036).