ORIGINAL ARTICLE

Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial

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ABSTRACT

Introduction Automatic titration modes of non-invasive ventilation, including average volume assured pressure support (AVAPS), are hybrid technologies that target a set volume by automated adjustment of pressure support (PS). These automated modes could offer potential advantages over fixed level PS, in particular, in patients who are super obese.

Methods Consecutive patients with obesity hypoventilation syndrome were enrolled in a two-centre prospective single-blind randomised controlled trial of AVAPS versus fixed-level PS using a strict protocolised setup.

Measurements The primary outcome was change in daytime arterial PCO_2 ($PaCO_2$) at 3 months. Body composition, physical activity (7-day actigraphy) and health-related quality of life (severe respiratory insufficiency questionnaire, SRI) were secondary outcome measures.

Results 50 patients (body mass index 50 ± 7 kg/m^2; 55 ± 11 years; 53% men) were enrolled with a mean $PaCO_2$ of 6.9 ± 0.8 kPa and SRI of 53 ± 17. 46 patients (23 AVAPS and 23 PS) completed the trial. At 3 months, improvements in $PaCO_2$ were observed in both groups (AVAPS $\Delta 0.6$ kPa, 95% CI 0.2 to 1.1, $p<0.01$ vs PS $\Delta 0.6$ kPa, 95% CI 0.1 to 1.1, $p=0.02$) but no between-group difference ($\Delta -0.1$ kPa, 95% CI -0.7 to 0.6, $p=0.87$). SRI also improved in both groups (AVAPS $\Delta 11$, 95% CI 6 to 17, $p<0.001$ vs PS $\Delta 7$, 95% CI 1 to 12, $p=0.02$; between groups $\Delta 5$, 95% CI -3 to 12, $p=0.21$). Secondary analysis of both groups combined showed improvements in daytime physical activity that correlated with reduction in fat mass ($r=0.48$; $p=0.01$).

Conclusion The study demonstrated no differences between automated AVAPS mode and fixed-level PS mode using a strict protocolised setup in patients who were super obese. The data suggest that the management of sleep-disordered breathing may enhance daytime activity and promote weight loss in super-obese patients. Trial registration details available at http://www.controlled-trials.com/ISRCTN63940700

Key messages

What is the key question?
► Does the addition of volume-targeted non-invasive ventilation (NIV) to standard fixed bi-level pressure support (PS) improve physiological and clinical outcomes in the treatment of stable obesity hypoventilation syndrome (OHS)?

What is the bottom line?
► There were no clinically important differences between volume-targeted NIV and fixed PS NIV when set up using a strict titration protocol in terms of improvement in gas exchange, daytime somnolence, health-related quality of life, and actigraphy assessed sleep and activity parameters.

Why read on?
► The study provides essential data for the clinician on the setup of NIV in OHS and confirms the improvements in gas exchange, daytime somnolence and health-related quality of life that occur with NIV therapy. It also demonstrates an objective improvement in daytime physical activity with the treatment of sleep-disordered breathing in OHS.

has become the commonest diagnosis for initiation of domiciliary non-invasive ventilation (NIV).[2] Data from physiological studies and controlled trials investigating the effect of continuous positive airways pressure (CPAP) and bi-level NIV in OHS have demonstrated improvements in daytime gas exchange and symptoms with both treatments.[3–6] A single-centre randomised controlled trial of selected patients with OHS controlled on CPAP showed equivalence between CPAP and NIV,[3] leading consensus opinion to advocate the use of NIV in patients whose condition is uncontrolled on CPAP.[7]

Patients who are obese and have sleep-disordered breathing have a disturbance of the respiratory muscle load—capacity—drive relationship, resulting in chronic respiratory failure.[8–10] We

INTRODUCTION

Although only first described as a case report in 1955,[1] obesity hypoventilation syndrome (OHS)

previously demonstrated that in patients who are obese movement from sitting to supine increases respiratory muscle load and neural respiratory drive, with an associated fall in tidal volume,[11] and this problem is further exaggerated through the different stages of sleep.[12] Conceptually, standard bi-level NIV with fixed-level pressure support (PS) delivery may not maintain adequate ventilation during the changes in pulmonary mechanics that occur throughout sleep, so automatic titrating hybrid ventilatory modes that target a pre-set volume by adjustment of PS may be more effective. These novel modes, including average-volume-assured PS (AVAPS), estimate the expiratory tidal volume and respond by adjusting the inspiratory positive airway pressure (IPAP) to maintain ventilation. Although a small trial has shown that AVAPS provided a greater reduction in nocturnal transcutaneous carbon dioxide ($tcCO_2$) compared with fixed-level PS NIV in OHS,[13] a subsequent study suggested that this improvement in ventilation was offset by greater sleep disruption as a consequence of the variation in PS delivered.[14] This randomised controlled trial was undertaken to investigate if automated volume-targeted PS ventilation was more effective in reversing daytime hypercapnia than fixed-level PS ventilation using a strict protocolised setup in patients who are super obese and have chronic respiratory failure. Some of the results of this study have previously been reported in abstract form.[15–17]

METHOD
All subjects provided written informed consent prior to enrolment. The study was approved by Guy's Research Ethics Committee. The study was registered prospectively on a publically accessible database (http://www.controlled-trials.com/ISRCTN63940700).

Subjects
Patients admitted to the Lane Fox Respiratory Unit, St Thomas' Hospital and to the Sleep and Ventilation Unit, Royal Brompton Hospital for either elective assessment of stable OHS or assessment following an episode of acute decompensated respiratory failure secondary to OHS were screened for study inclusion. Study inclusion criteria were body mass index >40 kg/m^2; daytime stable respiratory failure with $PaCO_2$ >6 kPa and pH >7.35; absence of another identifiable cause of hypoventilation; ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) >0.70; and FVC <70% predicted. The exclusion criterion was an inability to provide written informed consent.

Study design
The study was a single (subject) blind, prospective, randomised controlled trial. Patients were randomly allocated to either fixed bi-level PS or AVAPS mode. Both modes were delivered by a BiPAP synchrony device (Philips-Respironics, Murrysville, Pennsylvania, USA). Pre-randomisation minimisation was performed to avoid allocation bias; variables were body mass index (40–50 kg/m^2, 50–60 kg/m^2 and >60 kg/m^2), neck circumference (<45 cm and ≥45 cm), gender and clinical presentation (acute or elective).

Patient assessment and treatment titration
Patients underwent baseline assessments of spirometry (Microplus handheld spirometer, Cardinal Health, Dublin, Ohio, USA), arterial blood gas measurement and anthropometrics, including body composition measurements using the bioelectrical impedance method (Bodystat 1500, Bodystat Ltd, Isle of Man, UK). Health-related quality of life (HRQL) was assessed by the severe respiratory insufficiency questionnaire (SRI).[18] In addition, Epworth sleepiness score, fatigue severity score and visual analogue scales were recorded to assess self-reported sleep comfort, fatigue and physical activity levels. Following randomisation, patients underwent attended limited respiratory polygraphy, including oximetry and measurement of $tcCO_2$ (Tosca 500, Radiometer, Crawley, UK) using an a priori protocol (figure E1, online data supplement) with settings titrated to abolish apnoeas and snoring and to achieve adequate nocturnal respiratory control. Supplementary oxygen was provided to patients who met the criteria for daytime hypoxaemia (PaO_2 <7.3 kPa or <8 kPa with secondary features of hypoxia or right heart failure) at the lowest flow rate that corrected hypoxaemia (PaO_2>8 kPa). Once established on NIV, patients were discharged and followed up at 3 months. A subset of patients underwent assessment of sleep disruption and daytime activity using the Actiwatch-64 (Philips-Respironics), an accelerometer device that has been used previously to measure daytime activity in obesity[19] and to assess sleep patterns in respiratory sleep disorders.[20] The accelerometer was worn for the 7 days following initiation of NIV and the 7 days following the 3-month assessment. Details of actigraphy analysis are provided in the online data supplement.

Data analysis and statistics
The study was powered with daytime (>4 h post waking) $PaCO_2$ as the primary outcome variable. Fifty patients were targeted for recruitment based on detecting a difference in daytime $PaCO_2$ of ≥0.5 kPa between the AVAPS and fixed-level PS groups. This provided a power of 80% at the 5% significance level and incorporated an expected 15% dropout rate. Data were analysed using independent or paired t test if appropriate, unless demonstrably not normally distributed, in which case an appropriate nonparametric equivalent was used. Parametric data are presented as mean ± SD and non-parametric data as median (range). Correlation analyses were performed using Pearson's correlation test. For all analyses, a p value <0.05 was considered statistically significant. Data analyses were conducted using PASW statistics version 18 (SPSS, Chicago, IL, USA).

RESULTS
Sixty-two patients were screened for study participation. Fifty patients consented and underwent randomisation. Four patients (two from each group) withdrew during follow-up. Further details are provided in the CONSORT diagram (figure 1).

Baseline anthropometrics and sleep variables
The groups were matched for important variables at baseline (table 1).

Automated versus protocolised NIV titration
The median time to achieve satisfactory NIV setup was 2 days (range 1–4 days) for both groups. Nocturnal ventilatory control, assessed by overnight oximetry and $tcCO_2$, was similar in both the AVAPS and fixed-level PS groups (table 2). Three patients failed to reach the predetermined criteria for satisfactory ventilator setup (2/25 PS vs 1/25 AVAPS; p=0.6) due to an inability to tolerate the increase in IPAP or estimated tidal volume (Vte). These patients were discharged on the highest tolerated settings. Supplementary oxygen was required by six patients (4/25 PS vs 2/25 AVAPS; p=0.4).

Figure 1 Consort recruitment diagram for enrolment and follow-up. AVAPS, average-volume-assured pressure support; PS, pressure support.
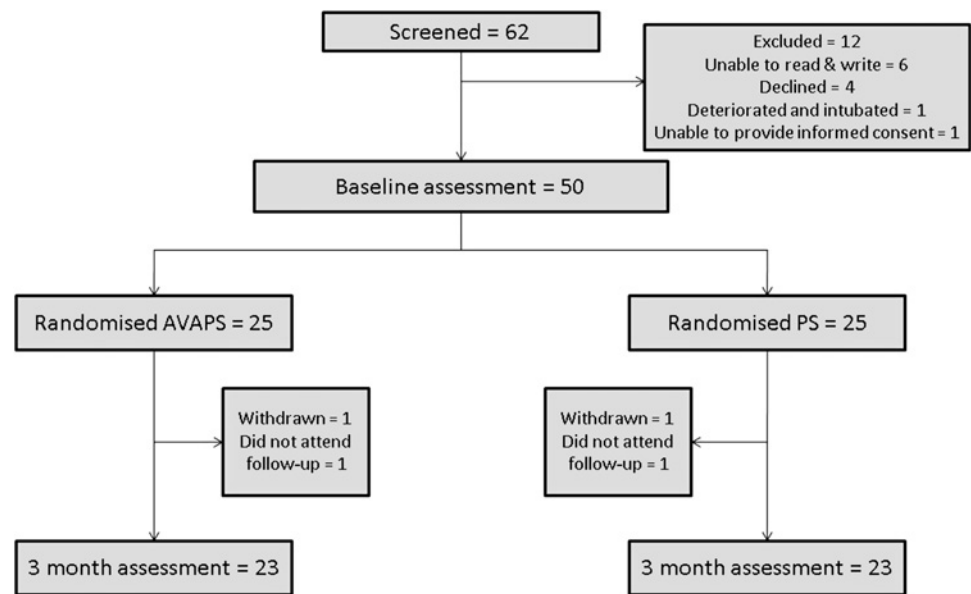
At discharge, ventilator settings provided a mean IPAP 25 ± 3 cmH$_2$O in the fixed PS group and mean Vte of 657 ± 96 ml in the AVAPS group. A small difference in mean expiratory positive airway pressure was shown with 10 ± 2 cmH$_2$O and 9 ± 1 cmH$_2$O in the fixed-level PS and AVAPS groups, respectively (p=0.03). Mean backup rate was 14 ± 1 breaths per minute in both groups.

Clinical presentation

The proportions of patients enrolled following an acute episode of decompensated hypercapnic respiratory failure were not significantly different between AVAPS and fixed PS groups (p=0.77). Further details are available in the online data supplement.

Actigraphy assessed sleep and physical activity parameters following initiation of NIV

There were no significant differences demonstrated between AVAPS and fixed-level PS groups in estimated total sleep time, wake after sleep onset time, sleep efficiency and sleep latency, at baseline or follow-up (table 3).

Outcome following 3 months of domiciliary NIV
Gas exchange, HRQL, daytime somnolence and control of sleep-disordered breathing

There were no-between group differences from baseline to follow-up in the primary outcome, PaCO$_2$, or secondary outcomes: daytime gas exchange, anthropometric measures, spirometry, HRQL or daytime somnolence (table 4 and table E1).

There were significant within-group improvements in PaCO$_2$ (table 1), HRQL (table 5), daytime somnolence, oximetry and tcCO$_2$ (figure 2) between baseline and follow-up.

There were no between-group differences in any of the assessed outcome variables (table 1) or ventilator parameters (table 6).

Anthropometrics and physical activity

Thirty-two patients completed actigraphy monitoring analysis at baseline and 28 patients at follow-up. There were no differences between the AVAPS and fixed-level PS group at either baseline or follow-up in measures of daytime physical activity and anthropometric variables (table E5).

Table 1 Clinical variables at baseline and at 3-month follow-up

	AVAPS			Fixed-level PS		
	Baseline	Follow-up	p Value	Baseline	Follow-up	p Value
Age (years)	53 ± 9			56 ± 11		
Gender (male/female)	12/13			11/14		
Emergency/elective presentation	9/16			9/16		
BMI (kg/m^2)	50 ± 8	48 ± 9	0.007	52 ± 8	51 ± 7	0.024
Fat-free mass (kg)	69 ± 17	68 ± 18	0.493	72 ± 18	71 ± 18	0.870
Waist circumference (cm)	141 ± 18	136 ± 17	0.006	145 ± 14	146 ± 14	0.120
Neck circumference (cm)	46 ± 6	46 ± 7	0.340	48 ± 5	48 ± 7	0.084
FEV$_1$ (% predicted)	53 ± 15	59 ± 14	0.039	55 ± 15	60 ± 16	0.222
FVC (% predicted)	52 ± 14	58 ± 13	0.019	56 ± 15	62 ± 18	0.189
PaCO$_2$ (kPa)	7.0 ± 0.7	6.4 ± 0.8	0.004	6.8 ± 0.8	6.2 ± 0.8	0.021
PaO$_2$ (kPa)	8.9 ± 1.2	9.1 ± 1.2	0.660	8.7 ± 1.8	9.3 ± 1.2	0.163
HCO$_3$ (mmol/litre)	31 ± 3	29 ± 3	0.001	31 ± 4	27 ± 3	0.003

The p values refer to paired t test analysis from initiation to follow-up values within each group.
AVAPS, average-volume-assured pressure support; BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; HCO$_3$, arterial concentration of bicarbonate; PaCO$_2$, arterial partial pressure of carbon dioxide; PaO$_2$, arterial partial pressure of oxygen; PS, pressure support.

Table 2 Comparison of oximetry—capnometry measurements prior to discharge following automated AVAPS setup and protocolised fixed-level PS setup

	AVAPS	Fixed-level PS	p Value
4% ODI (events/h)	22±16	22±17	0.517
Mean SpO_2 (%)	92±3	92±3	0.552
%TST <90% (%)	20±21	15±20	0.630
Mean $tcCO_2$ (kPa)	7.1±0.7	7.2±1	0.952
Max $tcCO_2$ (kPa)	8.4±0.8	8.4±1.6	0.980

The p value refers to comparison between interventions by independent t test.
AVAPS, average-volume-assured pressure support; % ODI, 4% oxygen desaturation index; PS, pressure support; SpO_2, oxygen saturation of haemoglobin; $tcCO_2$, transcutaneous carbon dioxide; %TST <90%, % total sleep time with SpO_2 under 90%.

Combined AVAPS and fixed-level PS cohort

As there were no clinically significant differences demonstrated between the AVAPS and fixed-level PS modes in either primary or secondary outcomes, a single cohort (n=28) was produced to allow a post hoc analysis of the relationship between physical activity and NIV in patients with OHS.

Physical activity and weight loss

Baseline data showed that patients spent an average of 3 h 21 min ± 1 h 33 min immobile or asleep during the daytime period. There were significant inverse correlations observed between daytime activity (mean activity counts per day), and weight (r=−0.39; p=0.02) and waist circumference (r=−0.42; p=0.01). Significant reductions in weight, fat mass and waist circumference were observed following 3 months of NIV, with an associated increase in physical activity (table 7).

There were correlations between change in physical activity, as measured by change in immobile time, and both the change in fat mass (r=0.48; p=0.01) and waist circumference (r=0.46; p=0.01) between baseline and follow-up assessment (figure 3).

Dose response to NIV

NIV showed a dose response effect with a significant correlation between hours of use and improvement in daytime $PaCO_2$ (r=−0.37; p=0.01) with the 95% CI crossing below 0 with an adherence time of 4 h (figure E2). Calculated mean Vte per kg ideal body weight (IBW) during the 3-month trial period correlated with change in daytime $PaCO_2$ (r=0.39; p=0.01) from baseline to follow-up (figure E3). These data indicate that 10 ml/kg IBW is the most appropriate ventilator setting in the AVAPS mode.

Backup rate and controlled nocturnal ventilation

Both the AVAPS and fixed-level PS groups had similar pre-set backup rates with similar levels of patient-triggered breaths. A post hoc analysis of the combined AVAPS and fixed-level PS cohort investigating the frequency of dependence on backup rate pressure controlled ventilation is provided in the online data supplement (tables E6—E8). Patients with a backup rate pressure controlled ventilation dependency >50% had a greater control of nocturnal carbon dioxide, improved daytime carbon dioxide and enhanced HRQL at 3 months.

DISCUSSION

This single-blind randomised controlled trial demonstrated that AVAPS ventilation has similar efficacy to fixed-level PS ventilation when accompanied by a strict protocolised setup in reducing daytime carbon dioxide level in patients with super obesity and OHS. These results are in contrast to previous data suggesting that automated variable PS provided enhanced nocturnal ventilatory control, but at a cost of increased sleep disruption. The current data represent the largest randomised controlled trial in patients with super obesity and chronic respiratory failure, and as such, these clinical data significantly add to the limited published data available. In addition, these data confirm the findings of previous small studies in patients who are less obese, demonstrating the improvements in daytime gas exchange, daytime somnolence and HRQL that can be achieved with the use of bi-level NIV. Furthermore in contrast to previous data, this study indicates that nocturnal treatment of chronic respiratory failure in patients who are super obese enhances daytime physical activity, which is associated with weight loss.

Table 4 Changes in gas exchange, anthropometrics, spirometry, daytime somnolence and HRQL between NIV initiation and follow-up

	AVAPS	Fixed-level PS	Mean difference between treatments (95% CI)	p Value
$\Delta PaCO_2$ (kPa)	−0.6±1.0	−0.6±1.1	0 (−0.7 to 0.6)	0.867
ΔPaO_2 (kPa)	0.2±1.7	0.5±1.6	0 (−1 to 1)	0.519
ΔHCO_3 (mmol/litre)	−3±3	−3±4	0 (−2 to 2)	0.825
ΔBMI (kg/m^2)	−1±2	−2±4	1 (−1 to 2)	0.497
ΔFat free mass (kg)	−1±6	0±8	−1 (−4 to 3)	0.805
$\Delta Waist$ circumference (cm)	−3±5	−2±7	−1 (−3 to 4)	0.676
ΔFEV_1 (% predicted)	6±13	4±14	2 (−6 to 10)	0.588
ΔFVC (% predicted)	6±12	5±17	1 (−7 to 10)	0.777
ΔESS (/24)	−5±6	−6±6	1 (−2 to 5)	0.428
ΔSRI-SS (/100)	11±12	7±13	5 (−2 to 12)	0.212

The p value refers to comparison between interventions by independent t test.
AVAPS, average-volume-assured pressure support; BMI, body mass index; ESS, Epworth Sleepiness Score (higher values indicate higher degrees of daytime somnolence); FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCO_3, arterial concentration of bicarbonate; HRQL, health-related quality of life; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PS, pressure support; SRI-SS, Severe Respiratory Insufficiency questionnaire summary score (higher values indicate better health-related quality of life).

Table 3 Actigraphy analysed sleep parameters for the first week following initiation of NIV compared with the first week following the 3-month assessment in the AVAPS (n=14) and fixed-level PS (n=15) arms

	Baseline			Follow-up		
	AVAPS	Fixed-level PS	p Value	AVAPS	Fixed-level PS	p Value
TST (min)	341±80	352±78	0.713	321±52	346±75	0.302
WASO%TST (%)	23±11	23±17	0.987	27±16	20±13	0.185
Latency (min)	5±3	8±7	0.164	4±2	5±6	0.577
Efficiency (%)	80±7	80±13	0.894	79±9	81±9	0.416

The p value refers to comparison between interventions at each time point by independent t test.
AVAPS, average-volume-assured pressure support; PS, pressure support; TST, total sleep time; WASO%TST, wake after sleep onset as a % of TST.

Table 5 HRQL pre—post treatment in AVAPS and PS groups

	AVAPS			Fixed-level PS		
	Baseline	Follow-up	p Value	Baseline	Follow-up	p Value
SRI-SS (/100)	55±16	66±19	<0.001	51±14	57±15	0.018
SRI-RC (/100)	55±20	70±20	0.001	49±24	59±22	0.025
SRI-PF (/100)	50±24	58±26	0.069	42±20	47±22	0.139
SRI-AS (/100)	48±17	62±20	0.003	48±19	54±16	0.100
SRI-SR (/100)	66±20	72±24	0.116	67±20	73±18	0.165
SRI-AX (/100)	48±24	65±29	0.001	41±23	50±21	0.094
SRI-WB (/100)	55±19	64±21	0.007	51±16	55±17	0.303
SRI-SF (/100)	61±24	73±20	0.005	55±22	63±22	0.143
VAS-sleep comfort (/100)	44±30	57±27	0.026	33±27	53±22	0.001
VAS-activity (/100)	43±24	52±26	0.177	47±23	47±22	0.967
VAS-fatigue (/100)	39±23	59±27	0.001	42±26	55±28	0.058
ESS (/24)	11±5	6±5	0.001	13±6	7±5	<0.001
FSS (/56)	43±14	34±15	0.014	45±16	37±18	0.038

The p values refer to paired t test analysis from initiation to follow-up values within each group.

AVAPS, average-volume-assured pressure support; ESS, Epworth Sleepiness Score; FSS, fatigue severity score (total=56; higher score indicates greater level of fatigue); HRQL, health-related quality of life; PS, pressure support; SRI-AS, Severe Respiratory Insufficiency questionnaire attendant symptoms and sleep; SRI-AX, Severe Respiratory Insufficiency questionnaire anxiety; SRI-PF, Severe Respiratory Insufficiency questionnaire physical functioning; SRI-RC, Severe Respiratory Insufficiency questionnaire respiratory complaints; SRI-SR, Severe Respiratory Insufficiency questionnaire social relationships; SRI-SS, Severe Respiratory Insufficiency questionnaire summary scale (total=100; higher score indicates higher quality of life); SRI-WB, Severe Respiratory Insufficiency questionnaire psychological wellbeing; SRI-SF, Severe Respiratory Insufficiency questionnaire social functioning; VAS, visual analogue scale (higher score indicates greater quality of life).

Critique of method
Study design
The study design used was a single-blind randomised controlled trial. The primary outcome was objective and all other assess-ments were conducted in accordance with international guide-lines, when available, or local policies to minimise the chance of assessor bias. This limitation is constant throughout other randomised studies in this area.[3] [13] Although the scientific

Figure 2 Pre—post treatment effect of pressure support (PS) and average-volume-assured pressure support (AVAPS) modes on data collected from combined oximetry—capnometry during ventilation: (A) nocturnal mean oxygen saturation (SpO_2) during ventilation; (B) % sleep time with SpO_2 <90% during ventilation; (C) mean transcutaneous carbon dioxide ($tcCO_2$) during ventilation; (D) maximum transcutaneous carbon dioxide ($tcCO_2$) during ventilation.
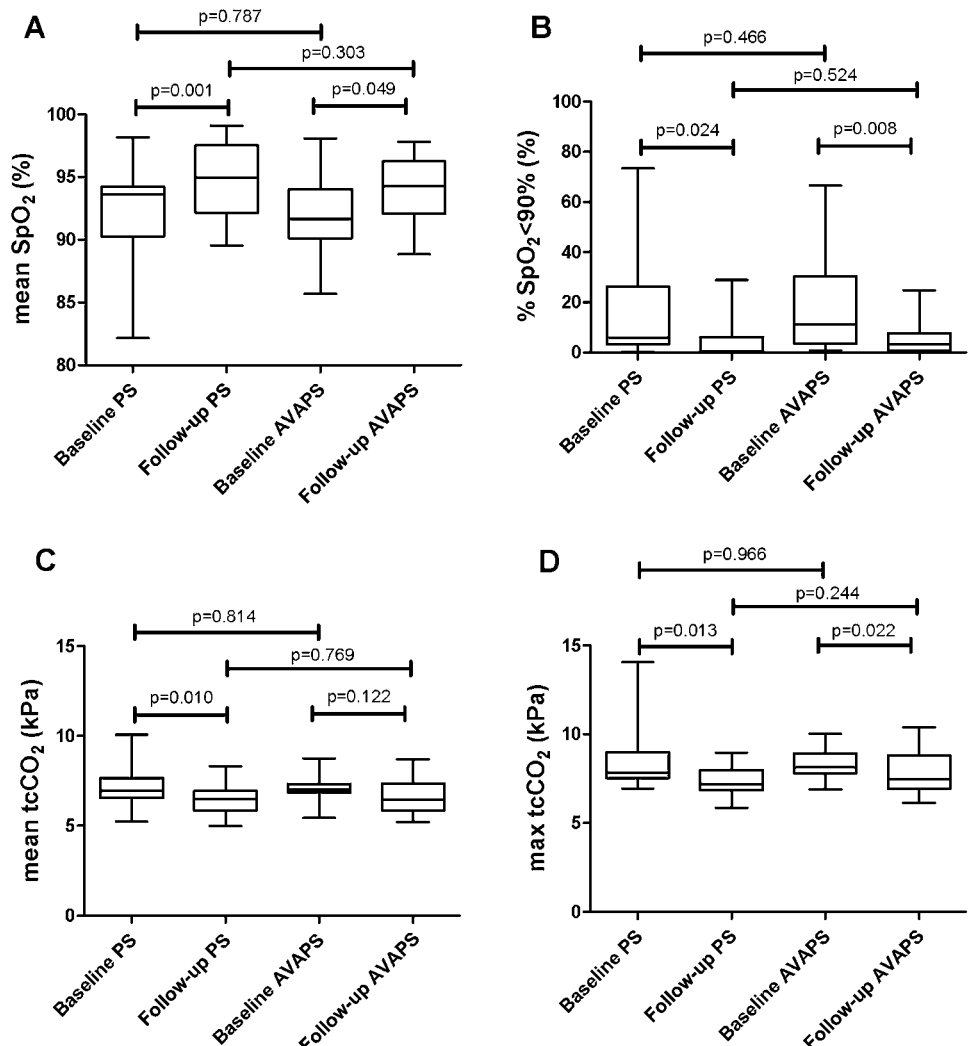
Table 6 Ventilator parameters at follow-up

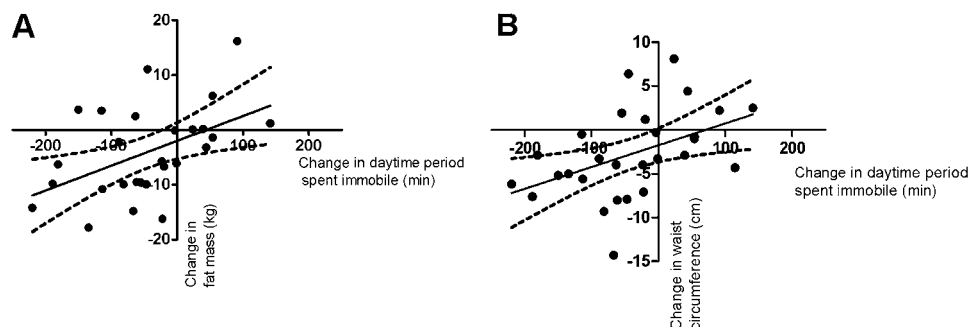|	AVAPS	Fixed-level PS	p Value
Delivered IPAP (cmH$_2$O)	22±5	23±4	0.402
Leak (litres/min)	53±13	53±19	0.968
Patient-triggered breaths (%)	43±27	45±27	0.759
Compliance (h:min/day)	4:11±02:53	5:08±02:22	0.230

AVAPS, average-volume-assured pressure support; IPAP, inspiratory positive airway pressure; PS, pressure support.

Table 7 Actigraphy (n=28) and anthropometric variables (n=46) at baseline and 3-month follow-up

	Baseline	Follow-up at 3 months	p Value
Weight (kg)	141±28	137±28	0.001
Fat-free mass (kg)	70±17	69±17	0.593
Fat mass (kg)	70±21	67±19	0.041
Waist circumference (cm)	142±15	140±16	0.003
Mean activity counts (counts/day)	232±100	263±94	0.016
Max activity counts (counts/day)	1797±507	2100±553	0.006
Immobile time (min/day)	201±93	161±84	0.028
Mobile time (min/day)	771±86	785±110	0.417

Actigraphy analysed for the first week at home following initiation of non-invasive ventilation (NIV) compared with the first week following the 3-month assessment of NIV.

quality of the current trial would have been enhanced by the addition of a third control arm, the clinical consensus and current evidence strongly support the use of domiciliary NIV in patients with significant nocturnal hypoxia and hypercapnia, such as were enrolled in this study. Furthermore, survival data from observational studies have demonstrated that in this patient population NIV confers a survival advantage and therefore we considered that the use of a control arm raised considerable clinical safety and ethical concerns.[21 22] This is the largest randomised controlled trial in this area and although it was designed with an 80% power there was a lower than expected dropout rate. However, the failure to demonstrate treatment superiority of AVAPS could occur as a result of a type 2 error.

Assessment methods

For the purposes of this study, we were focused on the primary outcome of change in PaCO$_2$ and differences in nocturnal ventilatory control between the AVAPS and the fixed-level PS, assessed and titrated using limited attended respiratory polygraphy. While it is considered ideal to confirm sleep and quantify sleep staging using extended polysomnography, this should not detract from the findings of the current trial. Previous studies have shown that oximetry—capnometry is an accurate method to monitor change in tcCO$_2$ in patients who are obese during NIV initiation.[23–26] The limitations of extended polysomnography to assess ventilator-induced sleep disturbance must also be highlighted. This approach only provides a single night assessment in a monitored hospital setting with a substantial array of electrocephalic, electromyographic and respiratory physiological monitoring equipment attached to the patient, all of which may cause sleep disruption. Despite the difficulties of assessing the disruptive effects of NIV on sleep, we aimed to investigate the effect of AVAPS and fixed-level PS on nocturnal disruption using 7-day actigraphy. As this technique collects data over multiple nights in the home, overcoming the nightly variation occurring with polysomnography,[27 28] it has been suggested to be a superior method of assessing treatment-associated sleep disruption in OSA.[29] Furthermore, actigraphy has been shown to be a valid method of assessing the sleep—wake cycle in patients with sleep-disordered breathing[30 31]

and the previously reported values for total sleep time, wake after sleep onset and sleep efficiency in patients with OHS using extended polysomnography are comparable with our current data.[13 14] Actigraphy has the added benefit of providing objective daytime physical activity data and in the current study it permitted interrogation of the relationships between nocturnal ventilatory control, daytime somnolence, physical activity and weight loss.

Applicability of findings

This study was designed to investigate the effects of a specific, propriety ventilator technology compared with a standard protocolised ventilator setup in OHS. There are, however, other devices incorporating pressure—volume hybrid ventilatory modes. Although working through the same fundamental principles, each of these differ in the exact method used to estimate and correct tidal volume. Therefore, the results of this trial are only applicable to the AVAPS mode and cannot necessarily be extrapolated to all such devices.

Significance of findings

Efficacy of ventilation

Both NIV modes provided similar control of nocturnal ventilation at baseline and follow-up. This was reflected as a similar improvement in hypercapnia at 3 months. These data are in contrast to previous studies demonstrating greater reduction in transcutaneous carbon dioxide during volume-targeted PS ventilation compared with fixed-level PS ventilation.[13 14] However, neither of the previous trials used a study titration protocol, as was used in the current study, to minimise the differences between the groups, and thus the ventilator setup favoured higher levels of PS delivered in the volume-targeted PS ventilation arm resulting in greater carbon dioxide clearance. In addition to previously published data, the data from this study showed that ≥4 h nocturnal ventilation was required to achieve

Figure 3 Correlations between change in daily physical activity as measured by daytime period spent immobile and (A) change in fat mass: r=0.48, p=0.01; (B) change in waist circumference: r=0.46, p=0.01.

a reduction in daytime carbon dioxide. These data are highly relevant to clinicians managing patients who are super obese to satisfactorily prescribe bi-level NIV.

Ventilation-induced nocturnal disruption

This study challenges previous data that showed volume-targeted PS ventilation contributes to sleep disruption during initiation of NIV in patients with OHS.[14] However, we consider our study design may explain this discrepancy because the previous studies used a crossover design, which is methodologically inferior to 1:1 randomisation. The patients were randomised in a crossover design to their 'normal' NIV with or without volume-targeted PS. Furthermore, the estimated tidal volume was based on the patients' actual body weight (8—10 ml/kg) rather than their IBW, which was the method used in the current study. Not unexpectedly, this study design resulted in a significantly higher mean IPAP in the volume-targeted PS group. Therefore, in addition to the unfamiliar mode of ventilation, these patients were provided with ventilator settings likely to negatively impact on sleep quality. In contrast, the current study had an a priori protocol for titration to produce similar delivered mean PS levels between the groups. Therefore, the data suggest that the differences demonstrated in earlier studies were inherent to study design and setup protocol rather than the treatment mode per se.

Improvements in HRQL, daytime somnolence and physical activity

Consistent with previous reports, there was a significant treatment effect resulting in improvements in daytime somnolence and HRQL.[3 13] There were no differences demonstrated in the magnitude of these improvements between groups, as expected, given that the efficacy of ventilation was similar. Our data suggest that nocturnal ventilatory support improves daytime symptoms and physical activity and that this is associated with weight loss in people who are obese. Interestingly, the observed change in body composition was a change in fat mass, rather than fat-free mass, indicating that it is not the result of the extracellular fluid clearance that would be expected to accompany the resolution of right ventricular dysfunction and cor pulmonale. The increased physical activity and reduction in weight accompanying the use of NIV for ≥4 h per night in patients who are super obese with OHS could potentially be enhanced by cardiopulmonary rehabilitation, and this needs to be considered in future studies.[32]

Conclusion

This single-blind randomised controlled trial showed that automated volume-targeted PS ventilation is as effective as standard fixed bi-level PS ventilation accompanied by a strict protocolised setup, producing similar improvements in nocturnal ventilatory control and daytime gas exchange, HRQL, daytime symptoms and daytime physical activity. In addition, the level of nocturnal disruption with both modes was similar. As a cohort sample, these data inform clinical practice by defining the duration of nocturnal NIV adherence to reduce daytime arterial carbon dioxide and improve daytime symptoms. Finally, this study has shown that improved control of sleep-disordered breathing in OHS was associated with an increase in physical activity and subsequent weight loss, highlighting the potential for augmenting this effect by the addition of an exercise programme.

Contributors Conception and design: NH, MIP, JM; data collection: PM; analysis and data interpretation: PM, NH, MIP, JM; manuscript drafting: PM, ACD, AS, MH, NSH, AJW, JM, MIP, NH.

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Journal club

Mouse lung regeneration after H1N1

This study demonstrates that following an ARDS-like syndrome in mice secondary to infection with a murine-adapted H1N1 virus, complete recovery follows the emergence of a population of stem cells bearing the differentiation markers of alveoli.

Contrary to the existing bleomycin-based models of pulmonary injury causing fibrosis, this murine H1N1 model sustains substantial airway damage and epithelial destruction, followed by viral clearing and histological recovery over several months. This represents a novel paradigm to investigate regenerative responses to infection.

Using molecular and immunohistochemical methods, the authors illustrate that following H1N1 infection, a cell population expressing p63, a known marker of stem cells in nasal and tracheal epithelia, emerges from distal bronchial epithelia in damaged lung and expands to form discrete 'pods' or islands of cells that concentrically surround distal airways. These pods assemble into novel alveoli-like structures bearing molecular markers and gene expression profiles of alveoli. Lineage tracing of these pods reveals a path originating in bronchiolar epithelium. Complete histological recovery including regeneration of alveoli—capillary networks follows over several months with no evidence of fibrosis. In parallel studies, the authors cultured comparable p63-positive stem cells derived from human distal airway epithelia, which similarly assembled into alveoli-like structures bearing specific molecular and genetic markers of alveolar and capillary development in vitro.

This work identifies a previously undescribed source of distal airway stem cells capable of regenerating damaged lung parenchyma following inflammation-induced lung injury, suggesting novel therapeutic approaches to currently non-reversible airway diseases. How the incipient alveoli-like structures integrate into existing airway structures remains to be seen.

▶ **Kumar PA**, Hu Y, Yamamoto Y, et al. Distal airway stem cells yield alveoli in vitro and during lung regeneration following H1N1 influenza infection. *Cell* 2011;**147**:525—38.

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                          ┌─────────────────────┐
                          │   Randomisation     │
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AVAPS
$IPAP = EPAP+4 - 30cmH_2O$
$EPAP = 8 - 10$
$Vte = 8 - 10ml/kg$ (ideal weight)
Ti 30-50% cycle
Back up rate = Resting rate - 4

PS
$IPAP = 18 - 22cmH_2O$
$EPAP = 8 - 10$
Ti 30-50% cycle
Back up rate = Resting rate - 4

Limited respiratory polygraphy including oximetry-capnometry
Satisfactory control of nocturnal hypoventilation (mean nocturnal SpO_2 >88% and a fall or rise <0.5kPa in $tcCO_2$) and abolition of obstructive events?

No

No

Yes

Increase Vte by 10% to improve hypoventilation
Titrate EPAP to abolish obstructive events (max 16)

Increase IPAP by 10% to improve hypoventilation
Titrate EPAP to abolish obstructive events (max 16)

Aims
Mean nocturnal SpO_2 >88%
Fall or rise <0.5kPa in $tcCO_2$
No snoring / upper airways obstruction

Discharge

Titration
$IPAP - 10\%$ to nearest $1cmH_2O$
$Vte - 10\%$ to nearest 10ml
$EPAP - 1cmH_2O$ steps with tandem increase in IPAP ($1cmH_2O$) or Vte (5-10%)
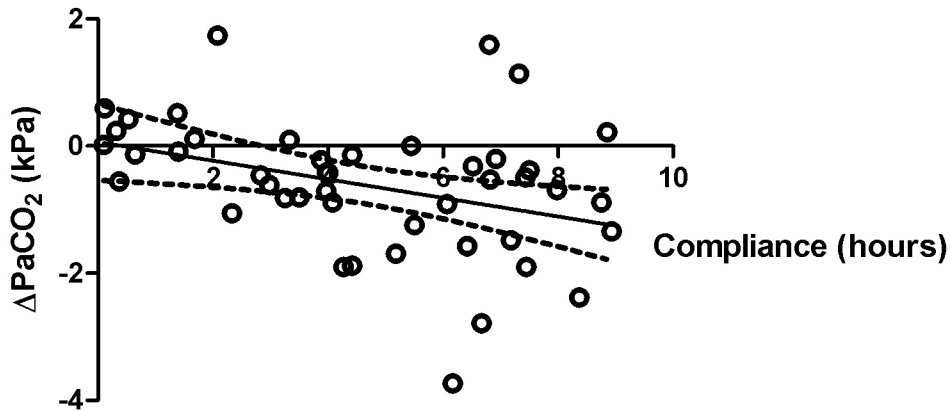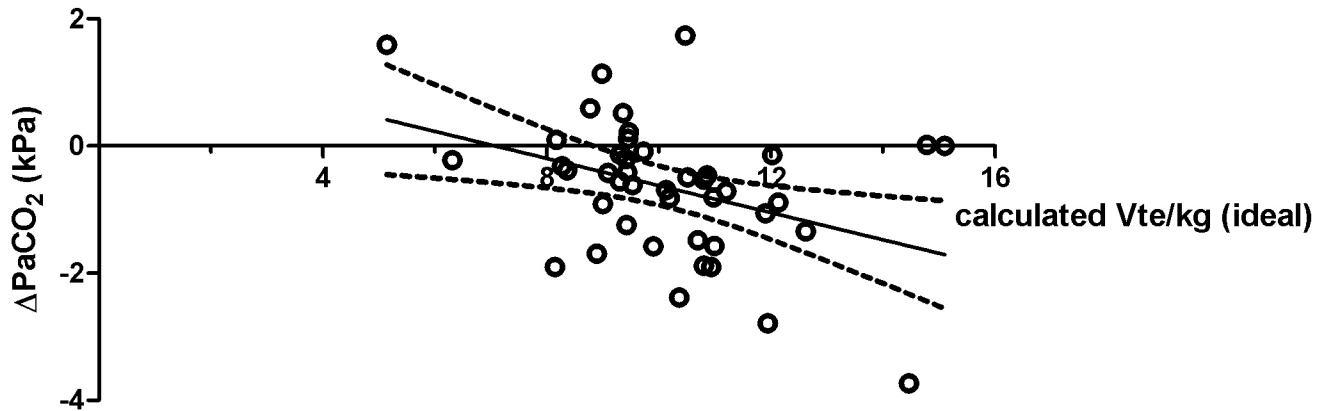
Volume Targeted versus Pressure Support Non-Invasive Ventilation

in Super Obese Patients with Chronic Respiratory Failure:

A Randomised Controlled Trial

– Online Data Supplement

METHOD

Ventilator setup

Following randomisation patients had ventilator parameters set according to the *a priori* protocol provided in Figure E1.

Sleep & Daytime Actigraphy

Patients were provided with an Actiwatch-64 (Philips-Respironics, Murrysville, PA, USA) mounted on the wrist of the patient's dominant arm via a standard strap with the investigator ensuring a firm fitting. Patients were provided with a 7-day sleep diary, and requested to record major and minor rest periods, and to use the device 'event marker' button to signal the start and finish of each day's major rest periods. Patients were requested only to remove the device for personal hygiene needs and to note the watch-free periods on the sleep diary. On completion of the 7-day recording the data from the devices were downloaded and analysed using Actiwatch-CT 5 software (Philips-Respironics, Murrysville, PA, USA). Major rest periods were set using a combination of the sleep diary, actogram and event markers for 7 consecutive days. Automated analysis calculated the following daily average values for:

Rest period

- Total sleep time (TST)

- Wake after sleep onset (WASO)

- Sleep efficiency

- Sleep latency

Active period

- Mean activity counts

- Peak activity counts

- Immobile time (minutes/day)

- Mobile time (minutes/day)

RESULTS

Outcome following 3 months of domiciliary NIV

Gas exchange, HRQL, daytime somnolence and control of sleep disordered breathing

Table E1: Between treatment group comparison of changes in HRQL between initiation of NIV and 3 month follow up.

	AVAPS	Fixed Level PS	Mean difference between treatments (95% CI)	p-value
△**SRI-SS (/100)**	11	7	5 (-2 – 12)	0.212
△**SRI-RC (/100)**	15	11	4 (-8 – 16)	0.464
△**SRI-PF (/100)**	8	5	3 (-7 – 14)	0.532
△**SRI-AS (/100)**	15	6	9 (-2 – 20)	0.121
△**SRI-SR (/100)**	5	6	0 (-11 – 10)	0.927
△**SRI-AX (/100)**	17	9	8 (-6 – 22)	0.260
△**SRI-WB (/100)**	9	4	5 (-5 – 14)	0.338
△**SRI-SF (/100)**	13	8	5 (-8 – 14)	0.429
△**VAS-sleep comfort (/100)**	13	20	8 (-8 – 23)	0.332

comfort (/100)				
∆VAS-activity (/100)	8	0	-9 (-26 – 9)	0.324
∆VAS-fatigue (/100)	19	13	-6 (-23 – 11)	0.480
∆ESS (/24)	-5	-6	1 (-2 – 5)	0.428
∆FSS (/56)	-9	-7	-2 (-11 – 8)	0.752

Abbreviations: SRI-SS - severe respiratory insufficiency questionnaire summary scale (total = 100; higher score indicates higher quality of life); SRI-RC - respiratory complaints; SRI-PF - physical functioning: SRI-AS - attendant symptoms & sleep; SRI-SR - social relationships; SRI-AX - anxiety; SRI-WB - psychological well-being; SRI-SF - social functioning; VAS - visual analogue scale (higher score indicates greater quality of life); ESS - Epworth sleepiness score; FSS - fatigue severity score (total = 56; higher score indicates greater level of fatigue). The p-value refers to comparison between interventions by independent t-test.

Clinical Presentation

NIV Initiation

Patients presenting acutely had similar baseline anthropometrics, but with a greater restrictive ventilatory defect on spirometry and more pronounced hypercapnia compared to those patients admitted electively for NIV set up (Table E2).

Table E2: Baseline data based on elective or acute clinical presentation.

	Elective (n = 33)	Acute (n = 17)	p-value
Treatment allocation (AVAPS / PS)	17/16	8/9	0.765
Age (years)	53±10	58±12	0.103
Gender (male / female)	16/17	11/6	0.276
BMI (kgm^{-2})	51±8	51±8	0.830
Fat Free Mass (kg)	71±18	71±20	0.944
Waist Circumference (cm)	140±14	149±19	0.079
Neck Circumference (cm)	47±5	48±6	0.348
FEV$_1$ (%predicted)	57±13	47±16	0.017
FVC (%predicted)	57±12	49±16	0.056
PaCO$_2$ (kPa)	6.7±0.6	7.3±0.8	0.004
PaO$_2$ (kPa)	8.7±1.1	8.9±2.2	0.796
HCO$_3$ (mmol/l)	30±3	32±4	0.149

Abbreviations: BMI - body mass index; FEV_1 - forced expiratory volume in 1 second; FVC - forced vital capacity; $PaCO_2$ - arterial partial pressure of carbon dioxide; PaO_2 - arterial partial pressure of oxygen; HCO_3 - arterial concentration of bicarbonate.

However, the differences in both gas exchange and spirometry were no longer significant at 6 weeks (p=0.36) and 3 months (p=0.94) follow up. Paradoxically, despite greater disease severity, patients presenting following an acute decompensated episode of respiratory failure reported higher levels in some health-related quality of life measures at enrolment and had larger improvements in some of these measures at follow up compared with those patients presenting electively. There were no significant differences between acute and elective groups in terms of length of time to setup (AVAPS 2 day ± 1 day vs. PS 2 day ± 1 day; p=0.4) or respiratory sleep study measures (Table E3).

Table E3: Comparison of limited attended respiratory polygraphy data for elective and acute clinical presentation at NIV initiation.

	Elective (n = 33)	Acute (n = 17)	p-value
4%ODI (events/hour)	25±18	17±10	0.085
Mean SpO_2 (%)	93±3	91±3	0.137
%TST<90%	18±23	16±15	0.708
Mean $tcCO_2$ (kPa)	6.7±0.7	7.4±1	0.061

| **Max tcCO$_2$ (kPa)** | 8.2±0.8 | 8.8±1.8 | 0.120 |

Abbreviations: 4%ODI - 4% oxygen desaturation index; SpO$_2$ – oxygen saturation of haemoglobin; %TST <90% - % total sleep time with SpO$_2$ under 90%; tcCO$_2$ - transcutaneous carbon dioxide; ns – not significant (p>0.1).

Variation in health-related quality of life

Differences, at both baseline and at 3-months follow up observed in health-related quality of life between patients presenting electively and those presenting following an acute decompensated episode of respiratory failure (Table E4).

Table E4: Health-related quality of life analysed according to elective and acute clinical presentation.

	Elective			Acute		
	Baseline (n=33)	Follow up (n=32)	p-value	Baseline (n=17)	Follow up (n=14)	p-value
SRI-SS **(/100)**	51±17	58±17	0.002	57±11	71±15[#]	0.003
SRI-RC **(/100)**	48±22	61±21	<0.001	62±19[#]	74±21[#]	0.094
SRI-PF **(/100)**	49±23	51±25	0.451	40±18	56±24	0.001
SRI-AS **(/100)**	44±17	53±17	0.012	58±15[#]	69±17[#]	0.017
SRI-SR **(/100)**	64±19	68±22	0.115	75±16	82±16[#]	0.180
SRI-AX **(/100)**	43±27	52±26	0.040	47±13	70±23[#]	0.003

SRI-WB (/100)	50±19	55±19	0.079	62±9[#]	69±17[#]	0.020
SRI-SF (/100)	60±22	74±19	0.064	56±22	66±23	0.018
VAS-sleep comfort (/100)	35±28	51±23	0.002	40±28	63±26	0.025
VAS-activity (/100)	42±24	42±22	0.986	51±18	66±21[#]	0.088
VAS-fatigue (/100)	35±21	50±24	0.003	50±25[#]	72±26[#]	0.046
ESS (/24)	12±6	7±5	<0.001	12±6	5±5	0.001
FSS (/56)	46±14	38±16	0.005	41±15	29±16	0.092

Abbreviations: SRI-SS - severe respiratory insufficiency questionnaire summary scale (total = 100, higher score indicates higher quality of life); SRI-RC - respiratory complaints; SRI-PF - physical functioning: SRI-AS - attendant symptoms & sleep; SRI-SR - social relationships; SRI-AX - anxiety; SRI-WB - psychological well-being; SRI-SF - social functioning; VAS - visual analogue scale (higher score indicates greater quality of life); ESS - Epworth sleepiness score; FSS - fatigue severity score (total = 56 higher score indicates greater level of fatigue). [#]independent t-test $p<0.05$ between group difference.

Ventilator settings showed a higher set IPAP in the PS arm in the acute (27±3 cmH$_2$O) compared to the elective (24±2 cmH$_2$O) group (mean difference 2.8 cmH$_2$O; 95%CI 0.4 to 5.2 cmH$_2$O; p=0.025). Set Vte was similar in both acute and elective groups in the AVAPS arm. A trend towards increased daily ventilator usage was observed in patients presenting acutely compared with elective presentation (mean difference 73 minutes; 95%CI -8 to 154 minutes; p=0.075) that translated into a significantly higher percentage of days with a ventilator usage of greater than 4 hours (mean difference 25%; 95%CI 7 to 45%; p=0.009). No significant between group differences were demonstrated in changes in gas exchange, respiratory sleep study parameters or anthropometric measures between baseline and follow up.

Daytime physical activity

Similar improvements were seen in the AVAPS and PS group in both changes in anthropometric and activity parameters between initiation and 3 month follow up (Table E5).

Table E5: Changes in actigraphy (n=28) and anthropometric (n=46) variables between baseline and 3 months follow up in treatment groups.

	AVAPS	Fixed Level PS	Mean difference between treatments (95% CI)	p-value
Δ**Weight (kg)**	-3±5	-5±9	2 (-2 - 7)	0.289
Δ**Fat free mass (kg)**	-1±6	0±8	-1 (-5 - 4)	0.805
Δ**Fat mass (kg)**	-2±7	-4±12	2 (-4 - 8)	0.484
Δ**Waist circumference (cm)**	-3±5	-2±7	-1 (-4 - 2)	0.676
Δ**Mean activity counts (counts/day)**	18±64	46±64	-28 (-78 - 22)	0.261
Δ**Max activity counts (counts/day)**	207±557	414±506	-207 (-624 - 209)	0.315
Δ**Immobile time (minutes/day)**	-39±96	-41±90	2 (-70 - 75)	0.947
Δ**Mobile time (minutes/day)**	4±93	24±79	-20 (-88 - 48)	0.545

Actigraphy analysed for the 1st week at home following initiation of NIV compared with the 1st week following the 3 month assessment of NIV

Ventilatory parameters

Dose Response

A dose response relationship was shown between mean daily ventilator adherence, as measured by ventilator data cards, and change in $PaCO_2$ (Figure E2) indicating greater improvements in gas exchange in patients with better ventilator adherence. A significant correlation was demonstrated when comparing the ventilator calculated mean Vte over the trial period and the change in daytime $PaCO_2$ (Figure E3).

Ventilator Triggering

Post hoc analysis of ventilator triggering was performed using data downloaded from ventilator data cards at the end of the study period. An arbitrary cut off of ≤ 50% and >50% non-triggered ventilator delivered breaths was selected to investigate the effect of back up rate pressure controlled ventilation (PCV) dependency on clinical outcome. Baseline data for the groups is provided below in Table E6.

Table E6: Comparison between patients receiving ≤ 50% pressure control ventilation (PCV) and those patients receiving > 50% PCV at baseline i.e. patient triggering greater than 50% of ventilator delivered breaths vs. less than 50% of ventilator delivered breaths.

	PCV ≤50% n=17	PCV>50% n=29	p-value
Age (years)	52±9	56±11	0.277
Gender (male / female)	7 / 10	16 / 13	0.840
$PaCO_2$ (kPa)	6.6±0.4	7.1±0.8	0.018
BMI (kg/m^2)	52±8	51±8	0.669
FEV_1 (% predicted)	57±15	54±15	0.558
FVC (%predicted)	53±17	52±15	0.791
ESS	11±6	13±6	0.400
SRI - summary score	51±16	54±16	0.532
Mean nocturnal SpO_2 (%)	93±3	92±3	0.105
Mean nocturnal $tcCO_2$ (kPa)	7.0±0.8	7.2±0.9	0.593

Abbreviations: $PaCO_2$ – arterial partial pressure of carbon dioxide; BMI – body mass index; FEV_1 – forced expiratory volume in 1 second; FVC – forced vital capacity; ESS – Epworth sleepiness score; SRI – severe respiratory insufficiency questionnaire; SpO_2 – oxygen saturation of haemoglobin; $tcCO_2$ – transcutaneous partial pressure of carbon dioxide..

The ventilator settings were similar at NIV initiation in each group as shown in Table E7.

Table E7: Comparison of ventilator settings between patients receiving ≤ 50% pressure control ventilation (PCV) and those patients receiving > 50% PCV at NIV initiation.

	PCV ≤50%	PCV>50%	p-value
IPAP (cmH$_2$O)	23±3	26±3	0.052
EPAP (cmH$_2$O)	9±1	10±2	0.047
Vte (ml)	619±75	661±96	0.301
Back up rate (bpm)	14±1	14±1	0.223

Abbreviations – PCV – back up delivered pressure control ventilation; IPAP – inspiratory positive airway pressure set in PS group; EPAP – expiratory positive airway pressure; Vte – estimated tidal volume set in AVAPS group.

Comparative *post hoc* analysis showed that patients with a back up rate PCV dependency >50% had a greater control of nocturnal carbon dioxide, improved daytime carbon dioxide and enhanced health-related quality of life at 3 months (Table E8). These data support the hypothesis that controlled NIV provides better nocturnal ventilatory control and improves patient outcome.

Table E8: Comparison of changes in gas exchange, anthropometrics, health-related quality of life and overnight oximetry-capnometry from baseline to 3 months in patients receiving ≤ 50% pressure control ventilation (PCV) and those patients receiving > 50% PCV at baseline.

	PCV ≤50% **n=17**	**PCV>50%** **n=29**	Mean difference between groups (95% CI)	p-value
Δ**PaCO$_2$ (kPa)**	-0.1±0.7	-1.0±1.1	0.9 (0.3 - 1.5)	0.003
Δ**BMI (kg/m^2)**	-0.3±1.5	-2.2±3.2	1.9 (0.2 - 3.6)	0.031
Δ**ESS**	-2±5	-8±6	6 (2 - 9)	0.001
Δ**SRI - summary score**	3±11	13±12	-10 (-2 - -17)	0.010
Δ**Mean nocturnal SpO$_2$ (%)**	3±6	5±4	-2 (-5 - 1)	0.146
Δ**Mean nocturnal tcCO$_2$ (kPa)**	-0.3±0.8	-0.9±1.2	0.6 (0.0 - 1.3)	0.049

Abbreviations – PCV – back up delivered pressure control ventilation; PaCO$_2$ – partial pressure of arterial carbon dioxide; BMI – body mass index; ESS – Epworth sleepiness score; SRI – severe

respiratory insufficiency questionnaire; SpO_2 – oxygen saturation of haemoglobin; $tcCO_2$ – transcutaneous partial pressure of carbon dioxide.

DISCUSSION

Clinical presentation

Patients with OHS may present both electively via sleep disorder, bariatric, and respiratory services or acutely following an episode of decompensated episode of acute on chronic respiratory failure. It is acknowledged that OHS is often a missed diagnosis, but it is less clear whether there are inherent demographic and other differences that influence the clinical presentation.   Patients were transferred following an acute episode after a period of stabilisation and we observed a lower vital capacity and worse hypercapnic respiratory failure in these patients.   An expected consequence of this was higher inspiratory pressures required during NIV set up to establish similar nocturnal oximetry and capnometry control.

Variations in patient self-reported health-related quality of life may, in part, explain the differences between elective and acute clinical presentation of our super obese cohort.   Patients presenting electively had greater impairment in terms of self-assessed respiratory complaints, sleep and attendant symptoms, and overall well-being. Patients presenting acutely had correspondingly higher levels, implying that these patients did not perceive the severity of their illness despite having greater physiological derangement at presentation. This lack of correlation between illness perception and physiological impairment is interesting. A rational assumption would be that patients with higher respiratory and sleep symptom burden would be more likely to seek medical attention electively, prompted by their symptoms, and this was reflected in the current data.   The variation in illness perception has significant implication to clinical services including emergency and critical care as well as bariatric services as simple symptom screening tools may lack sensitivity and

specificity to identify the patients at risk of acute deterioration. It may well be that screening spirometry, clinic oximetry and nocturnal home oximetry will provide greater sensitivity and specificity to screen super obese patients.

Changes in daytime physical activity

As there was no significant difference demonstrated between the intervention groups, we argued that combining them to produce a cohort study is scientifically valid and that this provides useful clinical outcome data determining the effect on nocturnal ventilatory control in a group of super obese patients with chronic respiratory failure. A reasonable hypothesis has been that there is a direct relationship between enhanced nocturnal ventilatory control and improvement in daytime symptoms which, in turn, has a direct relationship with an increase in daytime physical activity and weight loss. However, evidence for this has been lacking with few studies objectively assessing physical activity following resolution of hypersomnolence in patients with treated sleep-disordered breathing. The most recent data from a randomised controlled trial in male OSA patients with type 2 diabetes compared daytime physical activity using actigraphy in patients who received either therapeutic or sham-CPAP. There were no within or between group differences in physical activity levels.[1] Our study population differs from that studied by West *et al* as the patients in the current trial were eucapnic rather than hypercapnic as in the current study. Furthermore, half our cohort were female, and the patients in our cohort were substantially more obese. The West *et al* study failed to demonstrate an improvement in physical activity and there was also no weight loss achieved over the duration of the study in the study. This is, in contrast, to the 3% overall weight loss in our cohort. Although this level of weight loss appears minor, weight loss of this magnitude has been shown to be associated with improved

metabolic measures in diabetic patients.[2] The design of future studies of NIV to treat OHS will need to include such measurements.

Ventilatory parameters

Although it is expected that higher levels of pressure support result in greater ventilation, we hypothesised that those patients with lower ventilator triggering rates, and thus a higher proportion of pressure controlled breaths delivered by the ventilator, would have enhanced nocturnal ventilation. We indeed observed that these patients had marked improvements in nocturnal oximetry and capnometry measures, which was reflected in an enhanced improvement in HRQL between initiation and follow up compared to those patients who had higher triggering rates. Apart from a modestly higher $PaCO_2$ in the group more dependent on pressure control ventilation, the groups were reasonably matched at baseline in terms of anthropometrics, spirometry, daytime somnolence and health-related quality of life. As a *post-hoc* analysis the conclusions that can be drawn from these data are limited, however the data are hypothesis generating with the greater improvements in both night time and daytime gas exchange and HRQL in patients with greater dependence on back up rate pressure controlled ventilation. This warrants further investigation. It could be postulated that such patients are receiving ventilation that has driven the $PaCO_2$ below their apnoeic threshold and that this would be associated with more rapid re-setting of central respiratory drive and a subsequent improvement in clinical outcomes.   This approach could therefore be a more beneficial treatment strategy. Such data informs clinical practice and, in particular, suggests that clinicians might consider using a spontaneous-timed mode of ventilation in patients with OHS with a moderate back-up rate.

Automated titration vs. protocolised setup

The protocol used in the current study was designed to minimise the difference between each arm with the ventilator settings titrated in response to overnight oximetry and capnometry during attended limited respiratory polygraphy resulting in similar mean levels of delivered pressure support in each group. We observed no difference in the primary or secondary outcome parameters, indicating that automated volume targeted setup in the ward setting is equivalent to a strict in-hospital protocolised setup with fixed level PS. This provides important data for clinicians in smaller home mechanical ventilation units who do not have the manpower and facilities to incorporate a strict protocolised system with overnight modification of the ventilator settings to optimise setup. Such units could consider automated volume targeted titration as an alternative.

REFERENCES

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FIGURE LEGEND

Figure E1:

Post randomisation ventilator setup protocol.

Figure E2:

Demonstrates the relationship between mean nightly ventilator use and reduction in daytime $PaCO_2$ (arterial partial pressure of carbon dioxide) between randomisation and 3 month follow up.

Linear regression analysis with 95% confidence intervals of daily ventilator use in hours against change in $PaCO_2$ at follow up in patients allocated to both AVAPS and fixed level PS NIV. R= -0.37, p=0.01.

Figure E3:

Demonstrates the relationship between mean Vte per ideal body weight and reduction in daytime $PaCO_2$ (arterial partial pressure of carbon dioxide) between randomisation and 3 month follow up.

Linear regression analysis with 95% confidence intervals of ventilator calculated Vte/ideal body weight against change in $PaCO_2$ at follow up in patients allocated to both AVAPS and PS NIV. R= -0.39, p=0.01.