

## 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<sub>2</sub> (PaCO<sub>2</sub>) 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<sup>2</sup>; 55±11 years; 53% men) were enrolled with a mean PaCO<sub>2</sub> 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<sub>2</sub> were observed in both groups (AVAPS Δ0.6 kPa, 95% CI 0.2 to 1.1, p<0.01 vs PS Δ0.6 kPa, 95% CI 0.1 to 1.1, p=0.02) but no between-group difference (Δ−0.1 kPa, 95% CI −0.7 to 0.6, p=0.87). SRI also improved in both groups (AVAPS Δ11, 95% CI 6 to 17, p<0.001 vs PS Δ7, 95% CI 1 to 12, p=0.02; between groups Δ5, 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>

## INTRODUCTION

Although only first described as a case report in 1955,<sup>1</sup> obesity hypoventilation syndrome (OHS)

## 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).<sup>2</sup> 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.<sup>3–6</sup> A single-centre randomised controlled trial of selected patients with OHS controlled on CPAP showed equivalence between CPAP and NIV,<sup>3</sup> leading consensus opinion to advocate the use of NIV in patients whose condition is uncontrolled on CPAP.<sup>7</sup>

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.<sup>8–10</sup> We

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,<sup>11</sup> and this problem is further exaggerated through the different stages of sleep.<sup>12</sup> 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<sub>2</sub>) compared with fixed-level PS NIV in OHS,<sup>13</sup> a subsequent study suggested that this improvement in ventilation was offset by greater sleep disruption as a consequence of the variation in PS delivered.<sup>14</sup> 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.<sup>15–17</sup>

## 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<sup>2</sup>; daytime stable respiratory failure with PaCO<sub>2</sub> >6 kPa and pH >7.35; absence of another identifiable cause of hypoventilation; ratio of forced expiratory volume in 1 s (FEV<sub>1</sub>) 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<sup>2</sup>, 50–60 kg/m<sup>2</sup> and >60 kg/m<sup>2</sup>), 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).<sup>18</sup> 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<sub>2</sub> (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<sub>2</sub> <7.3 kPa or <8 kPa with secondary features of hypoxia or right heart failure) at the lowest flow rate that corrected hypoxaemia (PaO<sub>2</sub> >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<sup>19</sup> and to assess sleep patterns in respiratory sleep disorders.<sup>20</sup> 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<sub>2</sub> as the primary outcome variable. Fifty patients were targeted for recruitment based on detecting a difference in daytime PaCO<sub>2</sub> 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 non-parametric 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).

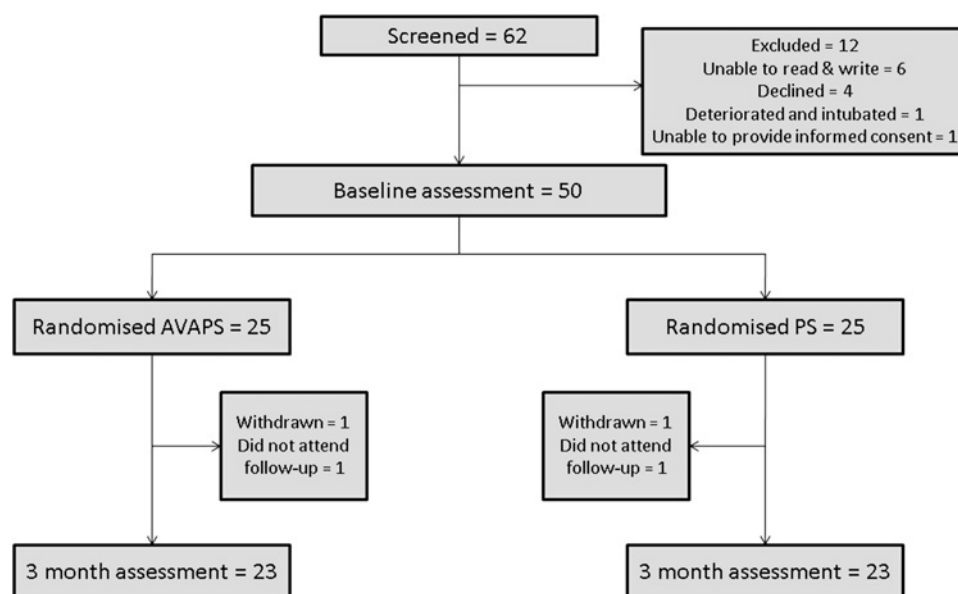
## Baseline anthropometrics and sleep variables

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<sub>2</sub>, 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 (V<sub>te</sub>). 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  $25 \pm 3$  cmH<sub>2</sub>O in the fixed PS group and mean V<sub>t</sub> of  $657 \pm 96$  ml in the AVAPS group. A small difference in mean expiratory positive airway pressure was shown with  $10 \pm 2$  cmH<sub>2</sub>O and  $9 \pm 1$  cmH<sub>2</sub>O in the fixed-level PS and AVAPS groups, respectively ( $p=0.03$ ). Mean backup rate was  $14 \pm 1$  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<sub>2</sub>, 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<sub>2</sub> (table 1), HRQL (table 5), daytime somnolence, oximetry and tcCO<sub>2</sub> (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 <sup>2</sup> )	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 <sub>1</sub> (% 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 <sub>2</sub> (kPa)	7.0±0.7	6.4±0.8	0.004	6.8±0.8	6.2±0.8	0.021
PaO <sub>2</sub> (kPa)	8.9±1.2	9.1±1.2	0.660	8.7±1.8	9.3±1.2	0.163
HCO <sub>3</sub> (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<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; HCO<sub>3</sub>, arterial concentration of bicarbonate; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; PaO<sub>2</sub>, 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 <sub>2</sub> (%)	92±3	92±3	0.552
%TST <90% (%)	20±21	15±20	0.630
Mean tcCO <sub>2</sub> (kPa)	7.1±0.7	7.2±1	0.952
Max tcCO <sub>2</sub> (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<sub>2</sub>, oxygen saturation of haemoglobin; tcCO<sub>2</sub>, transcutaneous carbon dioxide; %TST <90%, % total sleep time with SpO<sub>2</sub> 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<sub>2</sub> (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<sub>2</sub> (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

**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
ΔPaCO <sub>2</sub> (kPa)	-0.6±1.0	-0.6±1.1	0 (-0.7 to 0.6)	0.867
ΔPaO <sub>2</sub> (kPa)	0.2±1.7	0.5±1.6	0 (-1 to 1)	0.519
ΔHCO <sub>3</sub> (mmol/litre)	-3±3	-3±4	0 (-2 to 2)	0.825
ΔBMI (kg/m <sup>2</sup> )	-1±2	-2±4	1 (-1 to 2)	0.497
ΔFat free mass (kg)	-1±6	0±8	-1 (-4 to 3)	0.805
ΔWaist circumference (cm)	-3±5	-2±7	-1 (-3 to 4)	0.676
ΔFEV <sub>1</sub> (% 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<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; HCO<sub>3</sub>, arterial concentration of bicarbonate; HRQL, health-related quality of life; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; PaO<sub>2</sub>, 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).

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 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		p Value	Follow-up		p Value
	AVAPS	Fixed-level PS		AVAPS	Fixed-level PS	
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).

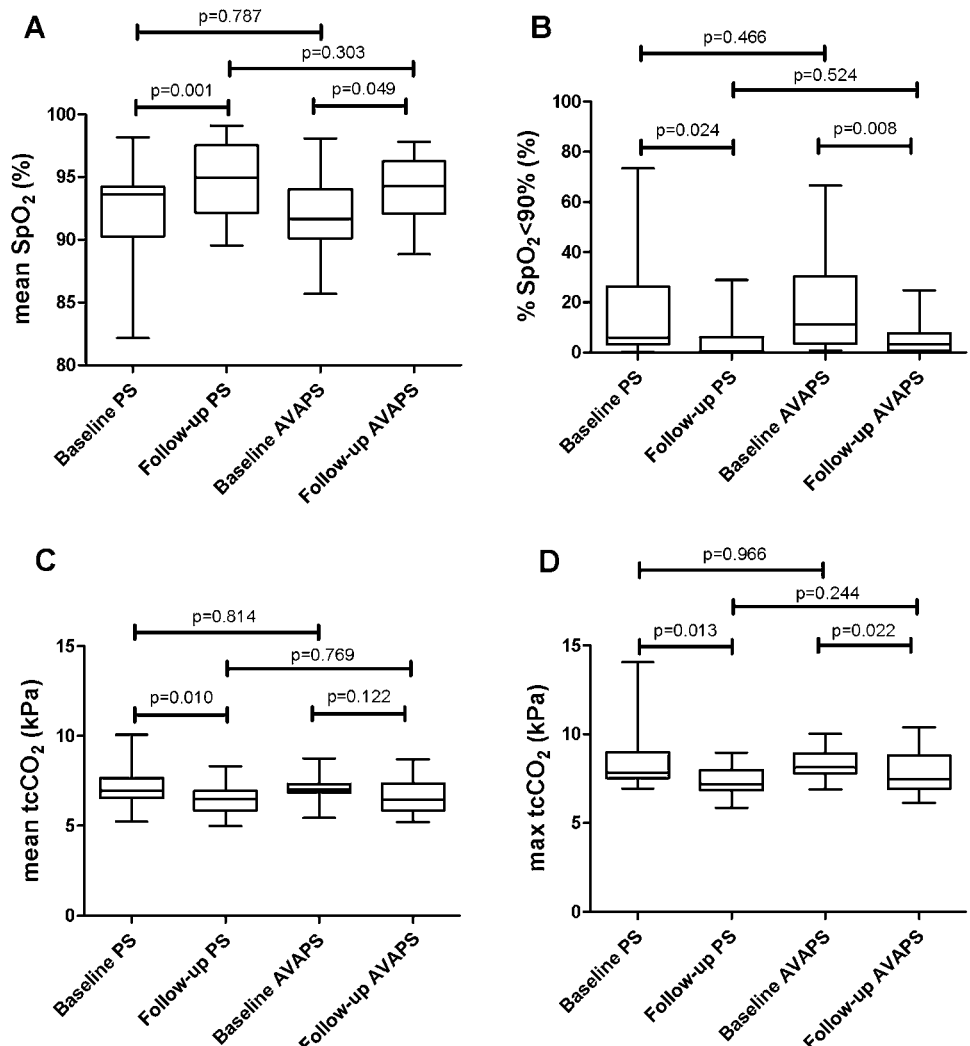
**Critique of method**

**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 guidelines, when available, or local policies to minimise the chance of assessor bias. This limitation is constant throughout other randomised studies in this area.<sup>3 13</sup> 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<sub>2</sub>) during ventilation; (B) % sleep time with SpO<sub>2</sub> <90% during ventilation; (C) mean transcutaneous carbon dioxide (tcCO<sub>2</sub>) during ventilation; (D) maximum transcutaneous carbon dioxide (tcCO<sub>2</sub>) during ventilation.



**Table 6** Ventilator parameters at follow-up

	AVAPS	Fixed-level PS	p Value
Delivered IPAP (cmH <sub>2</sub> 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

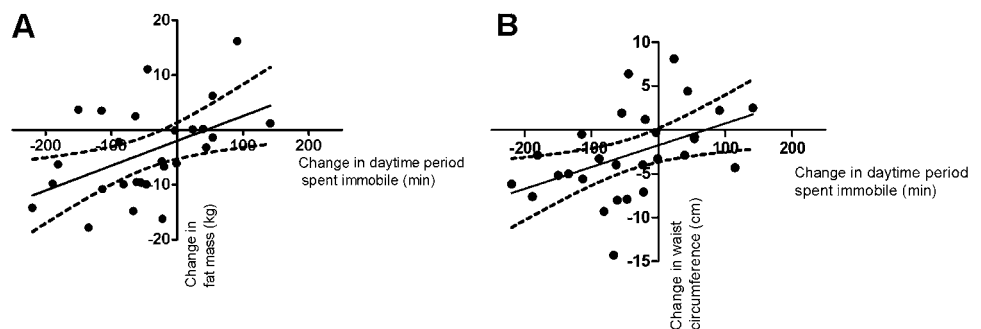
AVAPS, average-volume-assured pressure support; IPAP, inspiratory positive airway pressure; PS, pressure support.

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.<sup>21 22</sup> 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<sub>2</sub> 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<sub>2</sub> in patients who are obese during NIV initiation.<sup>23–26</sup> 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,<sup>27 28</sup> it has been suggested to be a superior method of assessing treatment-associated sleep disruption in OSA.<sup>29</sup> Furthermore, actigraphy has been shown to be a valid method of assessing the sleep–wake cycle in patients with sleep-disordered breathing.<sup>30 31</sup>

**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:  $r=0.46$ ,  $p=0.01$ .



**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.

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.<sup>13 14</sup> 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, proprietary 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.<sup>13 14</sup> 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

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.<sup>14</sup> 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.<sup>3, 13</sup> 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  $\geq 4$  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.<sup>32</sup>

### 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.

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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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