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	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_2O) compared to the elective (24±2 cmH_2O) group (mean difference 2.8 cmH_2O; 95%CI 0.4 to 5.2 cmH_2O; 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
∆Weight (kg)	-3±5	-5±9	2 (-2 - 7)	0.289
∆Fat free mass (kg)	-1±6	0±8	-1 (-5 - 4)	0.805
∆Fat mass (kg)	-2±7	-4±12	2 (-4 - 8)	0.484
∆Waist circumference (cm)	-3±5	-2±7	-1 (-4 - 2)	0.676
∆Mean activity counts (counts/day)	18±64	46±64	-28 (-78 - 22)	0.261
∆Max activity counts (counts/day)	207±557	414±506	-207 (-624 - 209)	0.315
∆Immobile time (minutes/day)	-39±96	-41±90	2 (-70 - 75)	0.947
∆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_2O)	23±3	26±3	0.052
EPAP (cmH_2O)	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
∆$PaCO_2$ (kPa)	-0.1±0.7	-1.0±1.1	0.9 (0.3 - 1.5)	0.003
∆BMI (kg/m^2)	-0.3±1.5	-2.2±3.2	1.9 (0.2 - 3.6)	0.031
∆ESS	-2±5	-8±6	6 (2 - 9)	0.001
∆SRI - summary score	3±11	13±12	-10 (-2 - -17)	0.010
∆Mean nocturnal SpO_2 (%)	3±6	5±4	-2 (-5 - 1)	0.146
∆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

1. West SD, Kohler M, Nicoll DJ, et al. The effect of continuous positive airway pressure treatment on physical activity in patients with obstructive sleep apnoea: A randomised controlled trial. Sleep Med. 2009;**10**:1056-8.

2. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;**22**:331-9.

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.