Randomised trial of CPAP vs bilevel support in the treatment of Obesity Hypoventilation Syndrome without severe nocturnal desaturation

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Running title: Positive pressure for OHS

Key words: Non-invasive ventilation, hypercapnia, quality of life, respiratory failure
ABSTRACT

**Background:** Untreated, obesity hypoventilation is associated with significant use of health care resources and high mortality. It remains unclear whether CPAP or bilevel ventilatory support should be used as initial management. The aim of this study was to determine if one form of positive pressure is superior to the other in improving daytime respiratory failure.

**Methods:** Prospective, randomised study of patients with obesity hypoventilation referred with respiratory failure. After exclusion of persisting severe nocturnal hypoxaemia ($S_pO_2<80\%$ for $>10$ minutes) or carbon dioxide retention ($>10\text{mmHg}$) despite optimal CPAP, patients were randomly assigned to receive either CPAP or bilevel support over a 3-month period. Primary outcome was change in daytime carbon dioxide. Secondary outcome measures included daytime sleepiness, quality of life, compliance with therapy and psychomotor vigilance testing.

**Results:** Thirty-six patients were randomized to either home CPAP ($n=18$) or bilevel support ($n=18$). The two groups did not differ significantly at baseline with regard to physiological or clinical characteristics. Following 3 months of therapy, daytime carbon dioxide levels decreased in both groups (CPAP $6\pm8\text{mmHg}$; bilevel $7\pm7\text{mmHg}$) with no between group differences. There was no difference in compliance between the two therapies (CPAP: $5.8\pm2.4\text{hrs/night}$ vs bilevel support: $6.1\pm2.1\text{hrs/night}$). Although both groups reported improvement in daytime sleepiness, subjective sleep quality and psychomotor vigilance performance were better with bilevel support.

**Conclusions:** Both CPAP and bilevel support appear to be equally effective in improving daytime hypercapnia in the subgroup of OHS patients without severe nocturnal hypoxaemia. The study was registered with the Australian Clinical Trials Registry (ACTRN0120500096651).

**Word count:** 253
INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder in the general, middle-aged population (1) with the prevalence rising rapidly as obesity increases (2). Despite significant sleep breathing abnormalities, the majority of patients with OSA and significant obesity are able to maintain normal daytime carbon dioxide levels. However, a small proportion of patients will develop hypercapnia in the absence of lung or neuromuscular disease, and be diagnosed as obesity hypoventilation syndrome (OHS). Recent work suggests around 1 in 10 patients presenting to a sleep laboratory are hypercapnic, with the prevalence rising as body mass index (BMI) increases (3). In a population of morbidly obese patients (BMI >40kg/m²) recruited from an obesity clinic, 23% were found to be hypercapnic (4). While the exact pathophysiologic mechanisms linking severe obesity with the development of daytime respiratory failure remain unclear, there is increasing evidence that timely and appropriate treatment of these patients is crucial in reducing the significant morbidity and mortality associated with this disorder (5, 6).

Both continuous positive airway pressure (CPAP) and bilevel ventilatory support (BVS) have been used clinically to manage patients with OHS (3, 7-9). Although many patients appear to respond to CPAP (10, 11), some do not (12, 13), and occasionally even more severe sleep disordered breathing can appear when obstructive events are abolished (14). With recent clinical trends towards limited diagnostic monitoring and home treatment of obstructive sleep apnea, it is possible that a significant number of patients with OHS may not be initially identified and consequently managed with CPAP alone. Therefore, understanding how such patients may respond to CPAP and how this compares to bilevel ventilatory support is an important clinical question. Furthermore, there has been limited investigation into changes in health related quality of life (HRQL) (11) and cognitive function in this group of patients once therapy is commenced. Therefore, the current trial was undertaken to determine if bilevel ventilatory support is more effective than CPAP in reversing daytime respiratory failure in patients with obesity hypoventilation without persisting severe nocturnal hypoxaemia. In addition, we wished to compare compliance with therapy, HRQL and neurocognitive performance between the two therapies. Preliminary results of this study have been presented in abstract form (15).

METHODS:

Subjects

Patients with obesity and daytime hypercapnia were recruited from the Sleep Disorders Clinic and Sleep Investigation Unit at Royal Prince Alfred Hospital. Inclusion criteria included: (1) obesity with a BMI >30kg/m²; (2) stable awake compensated respiratory failure with a PaCO₂ of ≥45mmHg and pH ≥ 7.34; (3) the absence of any significant respiratory, neuromuscular or other disorder that could account for the hypercapnia; (4) a FEV₁/FVC ratio ≥70%; (5) no major psychiatric illness that would affect the patient’s ability to participate in the study and (6) not currently being treated with positive pressure therapy. Based on clinical consensus and safety concerns a priori criteria were set so that, patients who displayed significant and prolonged desaturation or significant carbon dioxide retention during an initial CPAP trial were excluded from the study. These criteria were: i) oxygen saturation remaining below 80% continuously (> 10 minutes) in the absence of frank apnea ii) an acute rise in transcutaneous carbon dioxide (TcCO₂) (TCM3, Radiometer, Copenhagen, Denmark) during episodes of rapid eye movement (REM) sleep ≥ 10mmHg or iii) an increase in afternoon to morning PaCO₂ ≥ 10mmHg in those patients with an awake PaCO₂≥55mmHg. Figure 1 outlines patient screening and recruitment for the study. The study protocol was approved by the institutional review board of the Central Sydney Area Health Service (Protocol no. X03-0022) and written informed consent was obtained from all patients prior to entry into the study.
**Study Design**
Following routine baseline sleep studies, spirometry and arterial blood gases a CPAP titration was performed. Those patients meeting the above criteria for significant and prolonged desaturation or significant carbon dioxide retention during the initial titration night at best CPAP pressures were excluded from randomisation. The remaining patients where then randomly allocated to either longer term CPAP or bilevel therapy using opaque sealed envelopes.

Baseline evaluation performed prior to the CPAP titration night included anthropometric measurements and quality of life and sleep questionnaires, cognitive tests and psychomotor vigilance testing performed according to standard methods. Full details of these measurements and titration of positive pressure therapy are outlined in the online supplement. Patients were discharged home on positive pressure therapy for a 3-month period.

At follow up, baseline measurements were repeated and a CPAP titration was again performed to determine the patient’s current response to therapy. Results of this study along with arterial blood gases and compliance with therapy were then used to determine the patient’s longer-term home therapy.

**Analysis of data.**
The primary objective was to determine if there was a difference in change in daytime CO₂ levels between two different forms of positive pressure therapy, CPAP versus BVS, after a 3-month period of treatment. The secondary objectives included compliance with therapy, changes in quality of life and neurocognitive function.

An a priori power calculation suggested that a sample size of 13 in each group would be needed to detect a difference in arterial CO₂ of 7mmHg with a power of 80% and a p<0.05. Comparison between normally distributed parametric data was made using paired t tests for within group analysis. The Mann-Whitney U test was used for non-parametric data or non-normally distributed variables as indicated. The level of significance was taken as p<0.05. Analyses were performed using a commercially available statistical software package (SPSS version 14.0; SPSS; Chicago, IL).
RESULTS

Of the 85 subjects initially screened, 37 were excluded from the study. Reasons for exclusion are given in Figure 1, with acute respiratory failure the major reason. Three further patients were invited to participate in the study but declined: two felt they would not be able to return for follow up and one did not want to participate. This left 45 patients available for enrolment. Nine patients met the a priori criteria for outright initial CPAP failure and were treated with BVS on clinical grounds. The remaining 36 patients underwent randomisation, with 18 being allocated to CPAP and 18 to BVS.

Baseline anthropometric and sleep variables

Baseline characteristics of the two randomised groups did not differ, although fewer females were randomised to the CPAP group (Table 1). Likewise, there were no significant differences between groups with regard to sleep architecture, oxygenation or total respiratory disturbance index (Table 2).

Table 1 Baseline characteristics of patients studied.

<table>
<thead>
<tr>
<th></th>
<th>CPAP N=18</th>
<th>BVS N=18</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (yrs)</td>
<td>52±17</td>
<td>47±13</td>
<td>0.29</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>14:4</td>
<td>9:9</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>52±7</td>
<td>54±9</td>
<td>0.49</td>
</tr>
<tr>
<td>Awake SpO₂ (%)</td>
<td>90 [86-92]</td>
<td>87 [84-93]</td>
<td>0.86</td>
</tr>
<tr>
<td>Baseline PaCO₂, mmHg</td>
<td>52 [49-55]</td>
<td>49 [47-57]</td>
<td>0.36</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>30 [29-33]</td>
<td>30 [29-32]</td>
<td>0.56</td>
</tr>
<tr>
<td>FEV₁/FVC ratio (%)</td>
<td>81±6</td>
<td>81±7</td>
<td>0.72</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>50±4</td>
<td>51±5</td>
<td>0.53</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.99±0.09</td>
<td>0.97±0.13</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data presented as Mean±SD or median (interquartile range) as appropriate

Abbreviations: M, males; F, females; BMI, body mass index; BVS, bilevel ventilatory support; CPAP, Continuous positive airway pressure; SpO₂, oxygen saturation; PaCO₂, partial pressure of carbon dioxide; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; cm, centimetres.
Table 2  Baseline sleep and gas exchange data in all patient groups

<table>
<thead>
<tr>
<th></th>
<th>CPAP</th>
<th>BVS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum SpO2 (%)</td>
<td>55±14</td>
<td>53±20</td>
<td>0.75</td>
</tr>
<tr>
<td>%TST&lt;90 (%)</td>
<td>74 [52-99]</td>
<td>90 [57-100]</td>
<td>0.47</td>
</tr>
<tr>
<td>%TST&lt;80 (%)</td>
<td>19 [7-53]</td>
<td>13 [14-72]</td>
<td>0.28</td>
</tr>
<tr>
<td>TST (mins)</td>
<td>251 [108-333]</td>
<td>328 [259-345]</td>
<td>0.11</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>69 [42-87]</td>
<td>78 [65-84]</td>
<td>0.38</td>
</tr>
<tr>
<td>% NREM</td>
<td>88±7</td>
<td>87±8</td>
<td>0.67</td>
</tr>
<tr>
<td>% REM</td>
<td>12±7</td>
<td>13±8</td>
<td>0.67</td>
</tr>
<tr>
<td>NREM RDI (events/hr)</td>
<td>93 [59-112]</td>
<td>70 [19-97]</td>
<td>0.14</td>
</tr>
<tr>
<td>REM RDI (events/hr)</td>
<td>61 [57-91]</td>
<td>48 [30-68]</td>
<td>0.13</td>
</tr>
<tr>
<td>% hypopneas of TRDI</td>
<td>79 [25-87]</td>
<td>77 [45-92]</td>
<td>0.69</td>
</tr>
<tr>
<td>ESS</td>
<td>15 [8-17]</td>
<td>14 [12-19]</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data presented as Mean (SD) or Median [interquartile range] as appropriate

Abbreviations: BVS, bilevel ventilatory support; CPAP, Continuous positive airway pressure; SpO2, oxygen saturation; TST, total sleep time; NREM, non rapid eye movement sleep; REM, rapid eye movement sleep; ESS, Epworth Sleepiness scale; RDI, Respiratory disturbance index; TRDI, Total Respiratory disturbance index

**Initial response to CPAP**

Initial response to CPAP titration is outlined in Table 3. In seven of the 18 patients randomised to CPAP, initial response to CPAP was categorised as acceptable, while in the remaining 11 patients the response was incomplete with RDI remaining >10 events/hr or sustained oxygen desaturation >80% and <88% on best pressure. In the group randomised to BVS, the initial response to CPAP was acceptable in 11 patients. Mean home bilevel pressures used for the BVS group were IPAP 16±2cmH2O and EPAP 10±2cmH2O with all patients using a spontaneous mode of support. A full-face mask was used for home use in 13 patients (five allocated to BVS and eight on CPAP) while 23 patients used a nasal mask (13 on BVS and 10 using CPAP). In seven patients (three in the CPAP group and four in the BVS group) initial daytime and/or nocturnal oxygen (flow between 1-2L/min) was required to prevent SaO2 below 88%.
Table 3: Effect of initial CPAP therapy on overnight sleep parameters in patients allocated to longer term CPAP or BVS therapy.

<table>
<thead>
<tr>
<th>outcome</th>
<th>CPAP group</th>
<th>BVS group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective CPAP level (cmH2O)</td>
<td>14±3</td>
<td>13±2</td>
<td>0.65</td>
</tr>
<tr>
<td>Min SpO2 (%)</td>
<td>70±12</td>
<td>74±10</td>
<td>0.27</td>
</tr>
<tr>
<td>%TST&lt;90 (%)</td>
<td>39[16-80]</td>
<td>57[14-86]</td>
<td>0.66</td>
</tr>
<tr>
<td>AHI (events/hr)</td>
<td>22±29</td>
<td>13±12</td>
<td>0.22</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>73±18</td>
<td>80±12</td>
<td>0.18</td>
</tr>
<tr>
<td>% REM</td>
<td>23±12</td>
<td>22±12</td>
<td>0.75</td>
</tr>
<tr>
<td>Change TcCO2 NREM-REM (mmHg)</td>
<td>5±3</td>
<td>4±2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

^n=13; # n=15. Data presented as Mean (SD) or Median [interquartile range] as appropriate

Abbreviations: TcCO2 – transcutaneous carbon dioxide

Impact of 3-months positive pressure
Follow up data was available for all 36 patients randomised to therapy. At review both groups had experienced a reduction in weight of around 5kgs, improvement in daytime PaCO2 and a reduction in bicarbonate. However, there was no difference between therapies for any of these parameters (Table 4). Mean hours of nightly positive pressure use was not affected by the type of therapy the patient was allocated, with both groups using therapy more than 5.5 hours/night.

Table 4: Change in daytime gas exchange, weight and subjective sleep quality following 3 months of positive pressure therapy in the three treatment groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change in CPAP group</th>
<th>Change in BVS group</th>
<th>Mean difference between therapies</th>
<th>³ p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO2 (mmHg)</td>
<td>-5.8±8.4</td>
<td>-6.9±6.7</td>
<td>1.04</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>[95% CI: -4.5 to 6.6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake SpO2 (%)</td>
<td>6±3</td>
<td>8±5</td>
<td>1.9</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>[95% CI: -5.2 to 1.3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>-2.3±8.5</td>
<td>-2.5±2.5</td>
<td>0.2</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>[95% CI: -4.2 to 4.6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss (kgs)</td>
<td>-4.9±7.8</td>
<td>-5.6±9.4</td>
<td>0.7</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>[95% CI: -5.2 to 6.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean nightly therapy use (hrs)</td>
<td>5.8±2.4</td>
<td>6.1±2.1</td>
<td>0.33</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>[95% CI: -1.8 to 1.2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>-6±8</td>
<td>-9±5</td>
<td>2.89</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>[95% CI: -1.78 to 7.56]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td>-1.93±3.5</td>
<td>-5.6±3.9</td>
<td>3.67</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>[95% CI: 0.82 to 6.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

³ p-value denotes mean difference between CPAP and BVS treatment groups using unpaired t-tests p<0.05, ** p<0.001, within group changes from baseline
Subjective daytime sleepiness improved with treatment, with no difference between groups (Table 2). However, only those patients randomised to BVS experienced a significant improvement in subjective sleep quality (Table 4). Within group improvements in the SF-36 dimensions of Physical Functioning, Role–Physical, Vitality and Social Functioning were seen in the BVS group, while only Vitality improved in the CPAP group (Table 5). No treatment effect differences between the two groups in any dimension of the SF-36 questionnaire were seen (Table 5). Similarly, no treatment effect differences were found in the four performance tasks measured: Trails B, DSS, DSF or DSB. In the Psychomotor vigilance test, of the three metrics analysed only the mean of the slowest 10% of reaction times showed a significant treatment effect difference favouring BVS (p=0.03).

**Table 5: Changes in quality of life and neurocognitive testing following 3 months of positive pressure therapy.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change with CPAP</th>
<th>Change with BVS</th>
<th>p-value between group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>8 [-5 to 30]</td>
<td>24[0-35]</td>
<td>0.2</td>
</tr>
<tr>
<td>Role Physical</td>
<td>18[0 to 50]</td>
<td>31[0 to 50]</td>
<td>0.32</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>8[-10 to 26]</td>
<td>11[0 to 21]</td>
<td>0.51</td>
</tr>
<tr>
<td>General Health</td>
<td>10[-5 to 27]</td>
<td>9[0 to 16]</td>
<td>0.99</td>
</tr>
<tr>
<td>Vitality</td>
<td>14[-5 to 35]</td>
<td>26[12 to 45]</td>
<td>0.2</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>8[-25 to 25]</td>
<td>23[0 to 50]</td>
<td>0.12</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>4[0 to 33]</td>
<td>17[0 to 67]</td>
<td>0.5</td>
</tr>
<tr>
<td>Mental Health</td>
<td>13[0 to 28]</td>
<td>7[-8 to 24]</td>
<td>0.75</td>
</tr>
<tr>
<td>Physical combined score</td>
<td>7[-6 to 28]</td>
<td>20[9 to 34]</td>
<td>0.22</td>
</tr>
<tr>
<td>Mental combined score</td>
<td>12[8 to 19]</td>
<td>21[6 to 33]</td>
<td>0.28</td>
</tr>
<tr>
<td>PVT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapses</td>
<td>0.6 [0 to 0.5]</td>
<td>-2 [-4 to 0]</td>
<td>0.07</td>
</tr>
<tr>
<td>Median (ms)</td>
<td>9 [-16 to 27]</td>
<td>-21 [-29 to 0]</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean of Slowest 10% reaction times (1/rt)</td>
<td>0.07[-0.2 to 0.2]</td>
<td>0.32[0.05 to 0.5]</td>
<td>0.03</td>
</tr>
<tr>
<td>Trails B (secs)</td>
<td>-21[-34 to 0.5]</td>
<td>-2 [-20 to 17]</td>
<td>0.1</td>
</tr>
<tr>
<td>DSF</td>
<td>-0.3 [-1 to 0]</td>
<td>0.35 [-1 to 2]</td>
<td>0.16</td>
</tr>
<tr>
<td>DSB</td>
<td>0.08 [0 to 1]</td>
<td>0.5 [-1 to 2]</td>
<td>0.25</td>
</tr>
<tr>
<td>DSS</td>
<td>4 [0 to 8]</td>
<td>2 [0 to 6]</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Longer term management
Following 3 months of therapy, 30 patients were found to have a good response to nocturnal CPAP and were recommended this therapy long term. Four patients in the CPAP allocated group and two in the BVS group continued to show oxygen desaturation in REM sleep despite control of upper airway obstruction and were recommended bilevel support as long-term therapy.

DISCUSSION
This study compared the impact of CPAP and bilevel therapy on clinical outcomes in a subset of patients with obesity hypoventilation syndrome without severe CPAP resistant nocturnal hypoxaemia. While both CPAP and BVS have been used to treat OHS previously, this is the first study to compare the two modalities in a randomised fashion. Using daytime PaCO₂ as the primary outcome measure, we found no significant treatment effect differences between the two forms of positive pressure therapy, with both groups experiencing a significant fall in PaCO₂ with a mean difference of 1mmHg between groups. Likewise, no significant treatment effect differences could be found between groups with respect to weight loss, compliance with therapy or daytime sleepiness, with both groups experiencing similar improvements with treatment. The BVS treated group reported better subjective sleep quality and performed slightly better on a psychomotor vigilance task than the CPAP group. However, the clinical significance of these small differences is unclear. Both groups experienced significant improvements in the Vitality dimension of the SF-36, while the BVS group also had significant within group improvements in three other dimensions. However, no between group differences were seen.

There is limited data on the clinical outcomes following the introduction of positive airway pressure (PAP) therapy in patients with obesity hypoventilation. Currently, around 11% of OSA patients presenting to sleep laboratories are likely to be hypercapnic (3). However, with the increasing prevalence of obesity in the general population it is likely that these numbers will increase. With a move towards limited diagnostic monitoring and automated titration of obstructive sleep apnea, it is possible that some OHS patients, particularly those with less severe nocturnal hypoventilation and without overt signs of cardiorespiratory failure, may be treated initially with CPAP alone. In lab titration algorithms for PAP therapy in OHS have fairly uniformly suggested commencing in CPAP mode, with a switch to BVS if persistent desaturation below 88-90% in the absence of apneic events occurs (8, 13, 16). In most centres the titration and decision about ongoing therapy is based on a split night or single night titration. This study was undertaken to better understand the short-term consequences of maintaining OHS patients on CPAP, especially if a complete response to CPAP was not achieved during the initial titration study.

To our knowledge this is the first study to randomly assign patients with OHS to either CPAP or BVS to determine if there is a difference longer term in daytime hypercapnia or clinical outcomes between these two therapies, albeit in a specific subgroup of patients with OHS. One previous randomised crossover trial has investigated the impact of 6 weeks BVS in a spontaneous/timed mode (BVS-S/T) to BVS-S/T with average volume assured pressure support (AVAPS) in 10 patients with OHS failing initial CPAP therapy (17). Both forms of BVS were found to improve oxygenation, sleep quality and HRQL, with AVAPS providing a more efficient reduction in

Abbreviations: CPAP, Continuous Positive Airway Pressure; BVS, Bilevel ventilatory support; PVT, Psychomotor Vigilance test; DSF, Digit Span Forward; DSB, Digit Span Backwards; DSS, Digit Symbol Substitution
overnight TcCO₂ than standard BVS-S/T. However, the lower carbon dioxide during sleep did not translate into further clinical benefits with regards to sleep quality or HRQL. Interestingly, during both forms of BVS, desaturation index, arousal and hypopneas remained raised and were not different from that seen during the CPAP night. Therefore, despite significant residual sleep-breathing events on BVS, substantial clinical improvements in these patients were achieved. It could be argued that using a BVS mode with a back up rate may have yielded more significant differences between CPAP and BVS therapy in our study. However, using BVS in a S/T mode does not guarantee complete resolution of respiratory events or normalisation of sleep quality, with patient-ventilatory asynchrony or periodic breathing reported to occur frequently in stable OHS patients using this mode (18). The longer-term consequences of an incomplete response to either CPAP or bilevel support, especially during the initial titration night warrant further investigation.

In this current study, patients reported severely impaired health status prior to therapy. Significant within group improvements in vitality scores occurred with both forms of short-term PAP therapy. Significant within group improvements in other health dimensions were seen only in patients randomised to BVS (Physical Functioning, Role-Physical and Social Functioning). However, significant between group differences following therapy could not be demonstrated, probably due to the wide variability in responses and small study numbers. For many individuals irrespective of the therapy used, quality of life scores following therapy still remained significantly below that reported in a previous study of OHS patients following 3 to 6 months of CPAP therapy (11). As the patients reported here were massively obese with a mean BMI of around 52kg/m², this failure to normalise SF-36 dimension scores is not surprising and almost certainly due to the presence of other co-morbid conditions (5). However, use of a more disease-specific instrument may have identified more subtle differences between the two therapies not identified in a general tool like the SF-36. Future studies should more fully address quality of life issues in this population and the impact of different PAP therapies on health outcomes.

Compliance is obviously an important component of treatment success and this in turn relies on the patient’s tolerance of the therapy and the benefits they feel they derive from it. It has previously been argued that bilevel ventilation may be more comfortable than CPAP because the patient exhales against a lower mask pressure (19), and this would result in greater adherence with therapy. However, this has not been shown in OSA (20), and the current study has likewise failed to show any difference in nocturnal therapy use between the two therapies, with a mean nightly use of around 6 hours for both groups. This suggests that in OHS patients with predominantly upper airway obstruction, the type of PAP therapy is not a major factor associated with treatment compliance.

We arbitrarily reviewed patients after 3 months of therapy based on clinical practice (21). However, more recent data suggests that a 4-week period may be sufficient to achieve the full benefits of therapy with regard to changes in blood gases (7,16), irrespective of the type of PAP therapy used (16). Three months of therapy appeared to be a sufficient time period to allow improvements in nocturnal breathing such that a significant proportion of initial CPAP “incomplete responders” could be maintained on CPAP as long-term therapy. Other authors have also reported a substantial minority of patients who initially require bilevel support could be maintained out of respiratory failure by the long-term use of CPAP therapy (7,22). However, for other measures such as quality of life and neurocognitive function, it is possible that longer periods of time may be needed to achieve improvements and future research would need to address this issue.

A major limitation of this study is that results are applicable only to a subset of patients with OHS – those without severe persisting hypoventilation during initial CPAP titration. This limits the applicability of the findings to the entirety of OHS subjects. However, at the time of commencing this study there were safety concerns about continuing CPAP when severe sustained nocturnal hypoventilation persisted. Earlier data had indicated that untreated hypercapnia was associated with
a 4-fold increase in mortality among the severely obese\(^6\). Therefore, we believed it would be inappropriate to continue CPAP in those patients who continued to experience sustained severe oxygen desaturation or large rises in carbon dioxide despite control of upper airway dysfunction. However, the findings of this preliminary study have demonstrated that the short-term use of CPAP in OHS, even in those in whom nocturnal gas exchange and breathing abnormalities are not completely corrected during the first night of therapy, does not result in clinically significant differences in outcome compared to those placed on BVS. The patients currently reported had a high incidence of concomitant OSA in addition to their sleep hypoventilation. While this seems to be the case for the majority of patients with OHS\(^{23, 24}\), the results of this study cannot be extended to OHS patients presenting with purely sleep hypoventilation. Therefore, until results from larger randomised clinical trials in OHS patients with more severe sustained nocturnal hypoventilation are available, initial intervention with BVS with the possibility of transfer back to CPAP in the longer term would appear to be a reasonable and safe treatment approach in this patient group\(^{25}\). In addition, the sample size used in this study would be insufficient to detect differences in CO\(_2\) changes occurring between the two groups. However, there is currently no data to determine what is a clinically important change in daytime carbon dioxide in this population. Future studies would need larger sample sizes to examine more subtle differences between therapies and to follow subjects over longer time periods to determine the impact on HRQL and hospitalisations. Further discussion and outlining of study limitations are included in the online supplement.

In conclusion, we have demonstrated that both nocturnal CPAP and bilevel ventilatory support are equally effective in improving gas exchange in selected patients with OHS without initial severe persisting nocturnal hypoxaemia, with no treatment effect differences in weight loss, daytime sleepiness or compliance over a 3-month period. However, patients treated with bilevel support had significantly greater improvements in subjective sleep quality and reaction time compared to the CPAP group. The results of this study open the way for larger trials that include patients with more severe nocturnal hypoventilation in order to better define the role of CPAP and BVS in patients with OHS not only in the initial management of the disorder, but also on a longer term basis.
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COMPETING INTERESTS
The positive pressure devices used in this study were supplied by Air Liquide, Alexandria, Australia and Mayo Healthcare, Rosebery Australia. These companies were not involved in the design, data collection or interpretation of the findings of this study.
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Figure Legends:

Figure 1. Flow diagram outlining screening and recruitment of patients
References:


Subjects screened N=85

37 met exclusion criteria:
17 Acute respiratory Failure
4 Found not to be hypercapnic at repeat baseline ABGs
9 Already using CPAP therapy
3 Other possible contributors to hypoventilation – hemi-diaphragm paralysis and scoliosis/sarcoidosis
2 Major psychiatric disorders

Subjects eligible for enrolment N=48

Declined to participate N=3

Clinically managed on CPAP

Enrolled in trial N=45

Randomised group

Met a priori criteria for CPAP failure N=9

Randomised to CPAP N=18

CPAP for 3 mths N=18

Placed on BVS

Randomised to BVS N=18

BVS for 3 mths N=18

18 patients for analysis

18 patients for analysis

Figure 1
Randomised trial of CPAP vs bilevel support in the treatment of Obesity Hypoventilation Syndrome without severe nocturnal desaturation

Amanda J Piper, David Wang, Brendon J Yee, David J Barnes and Ronald R Grunstein.

On line Data supplement
Methods

Subjects
Patients with obesity and awake hypercapnia were recruited from the Sleep Disorders Clinic and Sleep Investigation Unit at Royal Prince Alfred Hospital over the period 2003-2005. Inclusion criteria to be enrolled in the study included: (1) obesity with a BMI ≥30kg/m²; (2) stable awake hypercapnic respiratory failure with a PaCO₂ of ≥45mmHg and pH ≥ 7.34; (3) the absence of any significant respiratory, neuromuscular or other disorder that could account for the hypercapnia; (4) a FEV₁/FVC ratio ≥70%; (5) no major psychiatric illness that would affect the patient’s ability to participant in the study and (6) not currently being treated with positive pressure therapy. Figure 1 outlines patient screening and recruitment for the study. Once patients agreed to participate, a CPAP titration was performed. Based on clinical consensus and safety concerns a priori criteria were set so that, patients who displayed significant and prolonged desaturation or significant carbon dioxide retention during this initial CPAP trial were excluded from the study.

Study Design
Following routine baseline sleep studies, spirometry and arterial blood gases to confirm the presence of awake hypercapnia, patients meeting the inclusion criteria were invited to participate in the study. The criteria for initial CPAP failure were i) oxygen saturation remained below 80% continuously despite the absence of frank apnea ii) an acute rise in transcutaneous carbon dioxide (TcCO₂) (TCM3, Radiometer, Copenhagen, Denmark) during episodes of REM ≥ 10mmHg or iii) an increase in afternoon to morning PaCO₂ ≥ 10mmHg in those patients with an awake stable PaCO₂>55mmHg. The remainder of the patients were then randomly allocated to either CPAP or bilevel therapy using opaque sealed envelopes. The randomisation process was the responsibility of a researcher not otherwise involved in the trial. Masking of treatment allocation was not possible.
Baseline evaluation included anthropometric measurements and quality of life and sleep questionnaires, cognitive tests and psychomotor vigilance testing. This evaluation was performed prior to the CPAP titration night. A short period of CPAP acclimatisation prior to the titration night was undertaken, which included mask fitting and use of CPAP at a range of pressures from 5-10cmH2O to ensure the patient understood the sensations they were likely to experience when using the therapy overnight. Overnight titration of CPAP was performed in all patients in a sleep laboratory using manual titration. Pressure was increased in 1cmH2O increments with the aim of preventing obstruction, flow limitation, desaturation and arousal. Those patients randomised to BVS then underwent a further trial to titrate appropriate bilevel pressure settings. During the bilevel titration, the EPAP was commenced at 2cmH2O below the pressure needed to abolish obstructive events during the CPAP titration or at 5cmH2O, whichever was higher. The EPAP was then increased in 1cmH2O increments if inspiratory efforts did not consistently trigger IPAP. The IPAP was initially set 4cmH2O higher than EPAP, and then increased to eliminate hypopneas and improve saturation. A spontaneous mode of bilevel support was used in all patients. Data regarding machine pressure and leak were obtained by passing the output signal from the machine either through external DC inputs into the polygraph system (Compumedics, Melbourne Australia) if using an AutoSet T/ VPAP II (ResMed, Bella Vista, Australia) or through an integrated therapy device control when using a REMStar Pro/ Duet LX (Respironics, Murrysville, USA) if an Alice Sleep system (Respironics, Murrysville, USA) was used. The protocol permitted the administration of supplemental home oxygen at 1-2L/min to maintain a SpO2>90% if SpO2 remained <88% in NREM sleep during the patient’s allocated home treatment study at the maximum pressure that eliminated obstructive apneic or hypopneic events.

Patients were then discharged home on positive pressure therapy (REMstar CPAP or Duet LX bilevel devices: Respironics, Murrysville, PA; S6 CPAP or VPAP II bilevel machines ResMed, North Ryde, Australia) for a 3-month period. A range of commercial masks were trialled with each
patient with the final choice dependent on comfort, fit and leak minimisation. A full-face mask was used for home use in 13 patients (five allocated to BVS and eight on CPAP) while 23 patients used a nasal mask (13 on BVS and 10 using CPAP). No routine review of the patients was scheduled, but they were encouraged to contact the clinical service if they were experiencing any problems with therapy, and to return to their local doctor and referring physician for ongoing medical management. All patients received general information and advice about of life style changes including weight loss and diet. However, adherence to this advice was not monitored by the investigators.

At 3 months patients returned for data collection and review. Anthropometric measurements, questionnaires and arterial blood gases were repeated in the afternoon, and machine hours were downloaded from the patient’s equipment. CPAP titration was again performed to determine the patient’s response to therapy. Results of this study along with arterial blood gases and compliance with therapy were then used to determine the patient’s longer-term home therapy.

The study protocol was approved by the institutional review board of the Central Sydney Area Health Service (Protocol no. X03-0022) and written informed consent was obtained from all patients prior to entry into the study. The study was registered with the Australian Clinical Trials Registry (ACTRN01205000096651).

Study Methods

All anthropometric measurements were performed with the subjects wearing light clothes without shoes. Waist and hip circumference was measured using standard techniques (1). The waist-to-hip ratio (WHR) was then calculated. Neck circumference was measured at the level of the cricothyroid cartilage.
Polysomnography was performed during the diagnostic and treatment nights using commercially available digital sleep systems (Profusion, Compumedics, Melbourne, Australia; or Alice 5, Respironics, Murrysville, PA, USA) following recognised guidelines \(^2\) and scored according to standard criteria \(^3\) by experienced sleep scientists unaware of the patient’s involvement in the trial. Nasal airflow was measured through a pressure transducer built into the sleep system, and recorded during both the diagnostic and CPAP titration nights. Scoring and analysis of respiratory events and arousals were performed for the diagnostic studies as well as both the initial and follow up CPAP studies.

A qualified sleep physician reviewed the de-identified sleep study report of the initial CPAP titration study for each randomised patient, and classified CPAP response as either “incomplete” or “acceptable” based on control of nocturnal respiratory events at best pressure (RDI<10 events/hr) and nocturnal oxygenation (>88% in the absence of apneic events)\(^4,5\).

Arterial blood gases were taken with the patient seated and breathing room air during the afternoon of their sleep study. Morning blood gases were taken following the CPAP titration night. Conventional spirometry was measured using a MicroLab portable spirometer (Micro Medical, Rochester, UK) while static lung volumes were performed using helium dilution (Morgan TLC, UK) in accordance with recommended guidelines \(^6\).

**Neurocognitive and quality of life measures**

Patients performed a 10-minute psychomotor vigilance test (PVT) \(^7\) to measure reaction times and vigilance, with the variables of Lapses (reaction time >500ms), Median reaction time and the Mean of the Slowest 10% reaction times reported. This latter metric was reciprocally transformed so that smaller numbers represented slower reaction times and larger numbers faster reaction times. Questionnaires related to quality of life and daytime sleepiness were also completed including the
Pittsburgh Sleep Quality Inventory (PSQI)\(^8\), the Epworth Sleepiness Scale (ESS)\(^9\) and the Medical Outcomes Study Short Form (SF-36)\(^10\). Neurobehavioural measures included the Trails B\(^11\) and Digit Symbol Substitution (DSS) tests\(^12\), used to assess cognitive performance in the domain of executive functioning and attention. Verbal memory was assessed with the Digit Span Backward (DSB) and Forward (DSF) tests\(^12\). Testing was performed at similar times at baseline and follow up.

Compliance with prescribed CPAP or bilevel therapy was taken from the hours of use as registered by an integrated hour meter within the machines.

**Analysis of data.**

The primary objective was to determine if there was a difference in the change in awake CO\(_2\) between two different forms of positive pressure therapy, CPAP versus BVS, after a 3-month period of treatment. The secondary objectives included compliance with therapy, changes in quality of life and neurocognitive function.

An a priori power calculation suggested that a sample size of 13 in each group would be needed to detect a difference in the mean change in arterial CO\(_2\) of 7mmHg with a power of 80\% and a p\(<0.05\). Comparison between normally distributed parametric data was made using an unpaired t test, and the Mann-Whitney U test was used for non-parametric data or non-normally distributed variables as indicated. The level of significance was taken as p\(<0.05\). Analyses were performed using a commercially available statistical software package (SPSS version 12.0; SPSS; Chicago, IL).

**Additional results:**
During CPAP titration, reliable TcCO2 data was obtainable from 15 patients in the BVS group and 13 patients in the CPAP group. In the remaining patients, large measurement drift, loss of signal or device failure precluded using TcCO2 with confidence. The available data showed a change in TcCO2 values from NREM to REM periods of $4 \pm 2$mmHg in the BVS group and $5 \pm 3$mmHg in the CPAP allocated group. This difference in CO2 retention during REM sleep when on CPAP was not different between groups ($p= 0.25$).

**Additional Discussion**

These preliminary results raise a number of interesting questions suitable for further investigation. We arbitrarily reviewed patients after 3 months of therapy based on previous clinical practice. However, more recent data suggests that a 4-week period may be sufficient to achieve the full benefits of therapy with regard to changes in blood gases, irrespective of the type of PAP therapy used. Three months of therapy appeared to be a sufficient time period to allow improvements in nocturnal breathing such that a significant proportion of initial CPAP “incomplete responders” could be maintained on CPAP as long-term therapy. Eighteen of the 36 patients studied were considered to have an incomplete initial response to CPAP, and would likely have been treated with BVS. However, after 3 months of therapy, only six patients required long term BVS. Other authors have also reported a substantial minority of patients who initially require bilevel support could be maintained out of respiratory failure by the long-term use of CPAP therapy. Although changes in blood gases appear to be stable by 3 months, it is possible that longer periods of time may be needed to achieve improvements in other measures such as quality of life and neurocognitive function, and future research would need to address this issue by utilising longer periods of therapy in comparison studies.

Another interesting issue is that of which mode of bilevel ventilatory support is most appropriate.
In this study, BVS in a spontaneous mode was compared to CPAP. There is significant variability in clinical practice with respect to the mode of BVS used in patients with OHS, with spontaneous (14, 15), spontaneous/timed (16) (S/T) and control modes of ventilatory support all being used by different centres (17, 18). It is not clear if greater differences between CPAP and BVS would have been seen if an S/T mode rather than a spontaneous mode had been used in this study. However, just as there is a lack of data comparing BVS to CPAP, there is also currently a lack of evidence to support one mode of ventilatory support over another. While it may be postulated that ineffective efforts or inconsistent triggering may occur spontaneous mode, rendering it less effective than S/T mode, there is currently no evidence to support this. One recent study of 20 patients with stable OHS treated with BVS S/T, significant respiratory events persisted during bilevel support, with patient-ventilator asynchrony seen in 55% of subjects, while 40% experienced a periodic breathing index >5/hr (18). While these events were not necessarily associated changes in nocturnal blood gases, they were associated with sleep fragmentation and reduced slow wave and REM sleep. The impact of this on longer-term clinical outcomes and quality of life parameters require further investigation, and comparison to CPAP therapy.

This study has a number of limitations. Firstly, patients were not blinded to the therapy they received. This was not possible given the study protocol where all patients underwent an initial CPAP titration in order to establish their immediate response to CPAP. In addition, it was not possible to blind all research staff to the group allocation of the patient. However, measurement and analysis of sleep studies, lung function and blood gases (the primary outcome measure) were carried out by staff not otherwise involved in the study. Secondly, and importantly, patients with severe persisting nocturnal hypoventilation despite CPAP were not randomised and this limits the findings of the study to a subgroup of individuals with OHS. At the time of commencing this study there were safety concerns about using CPAP alone with patients with OHS and severe nocturnal hypoventilation. Reports in the literature had identified significant worsening of gas exchange in
some patients when placed on CPAP\(^{(19)}\), and other data had indicated that untreated hypercapnia
was associated with a 4-fold increase in mortality among the severely obese\(^{(20)}\). Therefore, at the
time we believed it would be inappropriate to continue CPAP in those patients who continued to
experience sustained severe oxygen desaturation or large rises in carbon dioxide despite control of
upper airway dysfunction. Rather than using a more conservative clinical algorithm of switching to
bilevel support if SaO\(_2\) fell below 88-90% despite best CPAP titration\(^{(4,5)}\) we accepted continuous
oxygen desaturation to as low as 80%. However, the results from this current study can only be
applied to those OHS patients who do not demonstrate severe immediate failure of CPAP, defined
here as a sustained fall in saturation below 80%. Until results from appropriate randomised clinical
trials in OHS patients with more severe daytime respiratory failure are available, initial intervention
with BVS with the possibility of transfer back to CPAP in the longer term would appear to be a
reasonable and safe treatment approach. Finally, these patients had a high incidence of concomitant
OSAS in addition to their sleep hypoventilation. While this seems to be the case for the majority of
patients with OHS\(^{(21)}\), the results of this current study cannot be extended to OHS patients
presenting with purely sleep hypoventilation. Therefore, the results of this study cannot be
generalised to all patients with OHS
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