Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnoea syndrome

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ABSTRACT: The purpose of this study was to evaluate the effect of nasal continuous positive airway pressure (CPAP) on the abnormal ventilatory drive in hypercapnic patients with the obstructive sleep apnoea syndrome (OSAS).

Six patients with hypercapnic OSAS (Group I) and 24 patients with eucapnic OSAS (Group II) were studied. All patients had arterial blood gas analysis, overnight sleep studies, and an assessment of ventilatory drive (progressive hyperoxic hypercapnic response and progressive isocapnic hypoxic ventilatory response) prior to and during nasal CPAP therapy (at 2 weeks and 1 month of treatment).

Nasal CPAP effectively improved the hypopnoea/apnoea index in both groups (Group I: 87±14 vs 8±4; Group II: 63±17 vs 6±3). Both hypercapnic and hypoxic ventilatory drive before treatment were significantly impaired in Group I as compared to Group II. Both the slope and baseline level of the ventilatory response and the mouth occlusion pressure (P0.1) improved significantly after 2 weeks of nasal CPAP therapy in Group I, with normalization of arterial carbon dioxide tension (PaCO2) (6.3±0.2 to 5.2±0.4 kPa).

We conclude that it is possible to completely correct the abnormal ventilatory drive in hypercapnic OSAS patients within 14 days of initiating nasal CPAP therapy. Eur Respir J., 1994, 7, 2005–2010.

Pickwickian syndrome is characterized by daily hypersomnolence, secondary erythrocytosis, right-sided heart failure, and alveolar hypoventilation with hypercapnia during daytime wakefulness in obese hypercapnic obstructive sleep apnoea syndrome (OSAS) patients [1–3]. It has been suggested that hypercapnic OSAS patients experience greater oxygen desaturation during sleep than do those with eucapnic OSAS [4]. Abnormal hypoxic and hypercapnic respiratory drive has been reported in hypercapnic OSAS patients, in contrast to normal hypoxic and hypercapnic respiratory drive in eucapnic patients [5–7]. Therefore, an abnormal respiratory drive has been postulated to explain the clinical difference in these two sets of patients.

Both weight reduction [8, 9] and tracheostomy [10–12] can decrease work, and have been reported to be effective in improving ventilatory drive. Sullivan and Issa [10] showed that tracheostomy produced a left shift without a change in the slope of the ventilatory response versus arterial carbon dioxide tension (Paco2) line in two patients with severe OSAS [10].

Nasal continuous positive airway pressure (CPAP) is another effective therapeutic option for this disorder, before frank respiratory failure occurs [13]. Whilst there have been reports [14] of changes over time in the ventilatory response to CO2 with nasal CPAP therapy for OSAS, there are no data concerning response to hypoxia. Therefore, we designed this study to investigate the effect of nasal CPAP on both hypoxic and hypercapnic ventilatory drive in patients with hypercapnic OSAS.

Materials and methods

Subject selection

Group I consisted of 6 hypercapnic OSAS patients, Group II consisted of 24 patients with moderate to severe eucapnic OSAS (table 1). All 30 patients were selected for this study because they were co-operative and tolerated long-term nasal CPAP therapy well.

Group I patients were all characterized by obesity (with body mass index (BMI) greater than 35 kg·m⁻²), hypersomnolence on clinical evaluation, alveolar hypoventilation manifested by arterial hypoxaemia with carbon dioxide retention (Paco2 ≥ 6 kPa), erythrocytosis (haematocrit >55%), and clinical evidence of right ventricular heart failure. In addition, lung function as measured by simple spirometry was normal or nearly normal, and there was no history or clinical evidence of primary central nervous system, systemic or neuromuscular disease. None
of the subjects had evidence of acute infection for at least one month prior to the study. Alcohol or sedatives were avoided for at least one week before the overnight sleep study.

Sleep apnoea syndrome was diagnosed as a hypopnoea apnoea index (HAI)  \( \geq \) 5 by overnight polysomnography [15]. The HAI was defined as the mean number of hypopnoeas and apnoeas per hour of sleep. Mild OSAS was defined as an HAI 5, but <20; severe OSAS as an HAI 5, and lowest arterial oxygen saturation (SaO\(_2\)) <50%; and moderately severe OSAS as falling between the criteria for mild and severe OSAS. Apnoea episodes were defined as the absence of nasal and oral airflow for at least 10 s measured by thermistor, and absence of ventilation (summation of chest and abdominal excursion) greater than 10 s measured by a calibrated inductive plethysmography. Hypopnoea was defined as reduction in airflow measured by thermistor and reduction in ventilation (summation of chest and abdominal excursion) measured by a calibrated respiratory inductive plethysmograph, and reduction in tidal volume to below 50%, without a major change in respiratory frequency. The definition of apnoea and hypopnoea did not include a drop in SaO\(_2\) of greater than 4%. Central apnoea was defined as cessation of nasal and oral airflow with cessation of respiratory effort; respiratory effort being appreciated by both inductive plethysmography and diaphragm electromyography (EMG) from a surface electrode. Obstructive apnoea was defined as absence of nasal and oral airflow despite continuing respiratory effort. Mixed apnoea had both central and obstructive components, the obstructive part usually following the central. OSAS was diagnosed when obstructive and mixed apnoeas represented more than 80% of all apnoeic episodes.

Oxygen desaturation was defined as reduction in oxygen saturation of 4% or more from the baseline. Desaturation event frequency (DEF) was defined as the mean number of oxygen desaturation episodes per hour of sleep [15]. Arousal was defined as an increase in EMG tone for greater than 1.5 s, associated with a or o electronencephalographic (EEG) activity. Arousal index (AI) was defined as the mean number of arousals per hour of sleep. Movement index (MI) was defined as the mean number of leg movements per hour of sleep. Sleep was staged by the method of RECHTSCHAFFEN and KALES [16] on the basis of 30 s epochs.

To measure and calibrate the severity of snoring, a sound meter (Real-time sound level analyser, Model NA-23, Rion Co. Ltd, Tokyo, Japan) attached to a microphone was placed in the cricothyroid notch during each study. The sound channel was calibrated in the range 50–100 dB using a 1 kHz audiosignal. Only snores higher than 60 dB were counted; the total number of snores per hour of sleep was defined as the snore index (SI). The severity of snoring was also evaluated by the same experienced technician's observation as: 0 (no snoring); + (mild); ++ (moderate); +++ (severe); and ++++ (very severe).

### Ventilatory response testing

Ventilatory responses were measured between 3–5 p.m., with the subject seated. Progressive hyperoxic and hypercapnic ventilatory response was measured by the READ [17] rebreathing method. Progressive isocapnic and hypoxic ventilatory response was measured by the REBUCK and CAMPBELL [18] method. Minute ventilation

### Table 1. – Anthropometric and baseline spirometric and arterial gas values before, 2 weeks and 1 month after nasal CPAP treatment

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
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<tbody>
<tr>
<td></td>
<td>Before After 2 weeks</td>
<td>After 1 month</td>
</tr>
<tr>
<td>Age yrs</td>
<td>48±7</td>
<td></td>
</tr>
<tr>
<td>Sex M/F</td>
<td>5/1</td>
<td>-</td>
</tr>
<tr>
<td>Height cm</td>
<td>168±4</td>
<td>-</td>
</tr>
<tr>
<td>Body weight kg</td>
<td>111±9</td>
<td>-</td>
</tr>
<tr>
<td>Body mass index BW-Ht(^2)</td>
<td>39.1±2.4</td>
<td>-</td>
</tr>
<tr>
<td>Haemoglobin g·dl(^{-1})</td>
<td>17.4±0.5</td>
<td>-</td>
</tr>
<tr>
<td>Haematocrit %</td>
<td>56±0.6</td>
<td>-</td>
</tr>
<tr>
<td>FEV(_1)% pred</td>
<td>70±3.8</td>
<td>-</td>
</tr>
<tr>
<td>FEV(_1)/FVC %</td>
<td>84±4.0</td>
<td>-</td>
</tr>
<tr>
<td>PaO(_2), kPa</td>
<td>10.0±0.7</td>
<td>12.1±0.7†</td>
</tr>
<tr>
<td>PaCO(_2), kPa</td>
<td>6.3±0.2</td>
<td>5.4±0.4†</td>
</tr>
<tr>
<td>pH</td>
<td>7.4±0.03</td>
<td>7.4±0.04</td>
</tr>
<tr>
<td>Baseline SaO(_2) %</td>
<td>93±0.5</td>
<td>95±0.5</td>
</tr>
<tr>
<td>Mean SaO(_2) %</td>
<td>81±2.1</td>
<td>93±0.4†</td>
</tr>
<tr>
<td>Mean O(_2) desaturation interval s</td>
<td>48±6</td>
<td>15±2†</td>
</tr>
</tbody>
</table>

Data are presented as mean±sd. CPAP: continuous positive airway pressure; M: male; F: female; BW: body weight; Ht: height; FVC: forced vital capacity; FEV\(_1\): forced expiratory volume in one second; PaO\(_2\): arterial oxygen tension; PaCO\(_2\): arterial carbon dioxide tension; SaO\(_2\): arterial oxygen saturation. †: p<0.05 compared to before treatment. *: p<0.05 between groups I and II before treatment.
(obtained by integration of pneumotachograph flow) and mouth occlusion pressure over the first 100 ms of inspiration against an occluded airway \((P_{O_{1}})\) [19] were regressed linearly against the end-tidal carbon dioxide tension \((P_{CO_{2}})\) values or fall in \(Sao_{2}\) from baseline \((\Delta Sao_{2})\).

Sleep studies

Overnight sleep studies were performed by complete polysomnography. The recordings included EEG, electro-oculogram (EOG), submental EMG, bilateral tibial EMG, and electrocardiogram (ECG) from surface electrodes. Arterial oxygen saturation and heart rate were continuously measured using an Ohmeda pulse oximeter. Respiratory movement was monitored by inductance plethysmography, with transducers placed around the chest and abdomen. Nasal and oral airflow were monitored by thermocouple.

Arterial blood was drawn twice, on two separate days, and analysed for arterial oxygen tension \((Pao_{2})\), \(Paco_{2}\), and \(pH\). The average of the two results was used. Arterial blood gas (ABG) was measured before, 2 weeks and one month after nasal CPAP treatment.

After baseline studies, nasal CPAP (Respitronics) was used. Repeat respiratory drive studies were performed at 2 weeks and 1 month after beginning therapy. A repeat sleep study was also performed.

Data analysis

Student’s paired and unpaired t-test and the analysis of variance (ANOVA) test were used for statistical analysis, where appropriate. If the ANOVA test showed statistical significance, the Scheffe test was also done. All values are expressed as the mean±standard deviation, with significance accepted at \(p<0.05\).

Results

Groups I and II were well-matched by age and sex (table 1). Group I had a higher percentage of body mass index than Group II.

Baseline measurements

Group I had a lower forced vital capacity (FVC) than Group II, but there was no difference in the forced expiratory volume in one second \((FEV_{1})/FVC\). Group I also had a lower daytime \(Pao_{2}\), baseline \(Sao_{2}\) and mean \(Sao_{2}\), and a higher daytime \(Paco_{2}\) than Group II (table 1). There was no significant difference in \(pH\) between the two groups. Group I demonstrated higher haemoglobin and haematocrit values. There was a significant

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Fig. 1. – Comparison of baseline arterial oxygen saturation (Sao_{2}), lowest Sao_{2}, hypopnoea/apnoea index (HAI), desaturation event frequency (DEF), movement index (MI), arousal index (AI), and snore index (SI) between Group I and Group II, before and after nasal continuous positive airway pressure (CPAP) treatment (■: Group I before treatment; □: Group I after treatment; □: Group II before treatment; ■: Group II after treatment). There was significantly worse baseline Sao_{2}, lowest Sao_{2}, HAI and DEF in Group I than Group II before treatment (#: \(p<0.05\), unpaired t-test). There was also significant improvement of baseline Sao_{2}, lowest Sao_{2}, HAI and DEF, after treatment in both groups (*: \(p<0.05\), paired t-test), but there was no significant difference of MI, AI and SI, between the groups before or after treatment. However, these parameters improved significantly in both groups after treatment (*: \(p<0.05\)).
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difference in mean O$_2$ desaturation interval between the two groups before nasal CPAP treatment. The Pa$_O_2$, and Paco$_2$ were improved after 2 weeks and 1 month of nasal CPAP treatment in Group I patients, but not in the Group II patients. The mean Sa$_O_2$ and mean O$_2$ desaturation interval were improved after 2 weeks and 1 month of treatment in both groups. There was no significant change in FVC and FEV$_1$/FVC in either group before and after treatment (table 1).

**Sleep and sleep-associated breathing disorder data**

Group I patients had a more serious sleep breathing disorder and more severe nocturnal oxygen desaturation, as shown in the comparison of HAI, DEF and lowest Sa$_O_2$ (fig. 1). There were no differences in arousal index, movement index and snore index between the groups before nasal CPAP treatment (p<0.05) (fig. 1). Group I patients spent a longer percentage of total sleep time at lower Sa$_O_2$ values than did Group II (fig. 2).

Both groups had severely disturbed sleep architecture, with stage 1 and 2 sleep predominant, and very short periods spent in stage 3 and 4 deep sleep (fig. 3).

**Effectiveness of nasal CPAP therapy**

Treatment resulted in significantly improved sleep-related breathing disorder, particularly HAI (Group I: 87±14 vs 8±4; Group II: 63±17 vs 6±3) and DEF, (fig. 1), mean Sa$_O_2$ (table 1), lowest Sa$_O_2$, arousal index, snore index and sleep architecture in both groups of patients. There was no change in the percentage of time spent in rapid eye movement (REM) sleep before and after treatment in either group (fig. 3). Nasal CPAP also improved arousal index, movement index and snore index in both groups after treatment (fig. 1).

**Ventilatory response to hypercapnic and hypoxic stimulation**

Before nasal CPAP treatment baseline VE, P$_O_2$ and the ventilatory responses to hypercapnic or hypoxic stimulation was significantly lower in Group I subjects compared to Group II, which were within normal limits (table 2). After two weeks of nasal CPAP, Group I showed improvement in all parameters to both types of stimulation, achieving levels similar to Group II. No further improvements in baseline VE, P$_O_2$ or ventilatory response were noted after 1 month of therapy. In contrast, nasal CPAP did not alter these variables in Group II subjects.

**Correlations between ventilatory drive and HAI, mean Sa$_O_2$, lowest Sa$_O_2$, and Paco$_2$**

The data correlation between ventilatory drive and Paco$_2$, HAI, and mean Sa$_O_2$ are listed in table 3. Both hypercapnic and hypoxic ventilatory drive are significantly correlated with lowest Sa$_O_2$, Paco$_2$ and mean Sa$_O_2$. Group I had a lower ventilatory response to hypercapnia and hypoxia (table 2), greater HAI, and lower mean Sa$_O_2$ and Paco$_2$ than Group II (fig. 1 and table 1).
KUNITOMO  the waking hypercapnic ventilatory response [21–23]. Hypoxic stimulation. Severe sleep hypercapnia will blunt have reduced ventilatory response to hypercapnic and hypoxic stimulation. Patients with hypercapnia and/or hypoxaemia tend to explain hypoventilation in hypercapnic OSAS [5, 6].

Stoors and Dement [32] and Guilleminault and Rosekind [33] have shown that, in humans, sleep fragmentation alone worsens sleep apnoea and snoring. Whilst nasal CPAP did improve the sleep disturbance in our patients, there was no significant change in the time spent in REM sleep. This may have been due to technical reasons, such as first night effect on nasal CPAP, although Mahadevia et al. [34] has reported similar results, finding that the relative time spent in REM did not change significantly with CPAP.

Some very obese patients with a severe restrictive diaphragm movement, or patients with alveolar hypventilation syndrome, may require nasal bilevel positive airway pressure (BiPAP) or intermittent positive pressure ventilation (IPPV) by nasal mask. This does not negate our findings that, in those for whom nasal CPAP is effective, ventilatory responses can be normalized.

In the study by BERTHON-JONES and SULLIVAN [14], nasal CPAP resulted in a shift in the baseline but not in the slope of the ventilatory response to CO2 in hypercapnic OSAS patients. In our hypercapnic OSAS patients, both slope and baseline shifted toward normal in response to nasal CPAP. Improvement of ventilatory response may reflect improvements in sleep efficiency, latency and architecture. Stoors and Dement [32] and Guilleminault and Rosekind [33] have shown that, in humans, sleep fragmentation alone worsens sleep apnoea and snoring. Whilst nasal CPAP did improve the sleep disturbance in our patients, there was no significant change in the time spent in REM sleep. This may have been due to technical reasons, such as first night effect on nasal CPAP, although Mahadevia et al. [34] has reported similar results, finding that the relative time spent in REM did not change significantly with CPAP.

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In a large series of OSAS patients studied by KRIEGER et al. [30] hypercapnia was related to airway obstruction as well as to body weight. In order to control for this variable, we excluded all cases with FEV1/FVC <75%. Both LEECH et al. [31] and Guilleminault and Cummskey [12] have also reported series with no differences in FEV1/FVC between eucapnic and hypercapnic subjects.

Table 2. – Ventilatory and occlusion pressure response to hypoxia and hypercapnia before and after beginning nasal CPAP treatment

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before 2 weeks</td>
<td>After 1 month</td>
</tr>
<tr>
<td><strong>Hypercapnic response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline VE l min⁻¹</td>
<td>4.2±1.2</td>
<td>7.1±1.4 †</td>
</tr>
<tr>
<td>∆VE/Paco2 l min⁻¹ kPa</td>
<td>0.46±0.20</td>
<td>2.46±0.51 †</td>
</tr>
<tr>
<td>Baseline Pco2 cmH2O</td>
<td>0.4±0.2</td>
<td>0.9±0.2 †</td>
</tr>
<tr>
<td>∆Pco2/Paco2 cmH2O/kPa</td>
<td>0.05±0.02</td>
<td>0.28±0.11 †</td>
</tr>
<tr>
<td><strong>Hypoxic response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline VE l min⁻¹</td>
<td>4.5±1.4</td>
<td>6.9±0.11 †</td>
</tr>
<tr>
<td>∆VE/Sao2 l min⁻¹ %Sao2</td>
<td>-1.49±0.45</td>
<td>-2.81±0.86 †</td>
</tr>
<tr>
<td>Baseline Paco2 cmH2O</td>
<td>0.4±0.2</td>
<td>0.9±0.2 †</td>
</tr>
<tr>
<td>∆Paco2/Sao2 cmH2O/%Sao2</td>
<td>-0.08±0.03</td>
<td>-0.25±0.07 †</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *: p<0.05 between groups I and II before treatment. †: p<0.05 compared to before treatment.

ANOVA: analysis of variance; VE: minute ventilation; P0.1: mouth occlusion pressure; ∆: difference. For further abbreviations see legend to table 1.

Table 3. – Simple correlation coefficients of HAI, mean Sao2, Paco2 and hypercapnic and hypoxic ventilatory response

<table>
<thead>
<tr>
<th></th>
<th>Hypercapnic response</th>
<th>Hypoxic response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∆VE/Paco2</td>
<td>∆Pco2/Paco2</td>
</tr>
<tr>
<td>HAI</td>
<td>-0.42</td>
<td>-0.29</td>
</tr>
<tr>
<td>Mean Sao2</td>
<td>0.50</td>
<td>0.47</td>
</tr>
<tr>
<td>Lowest Sao2</td>
<td>0.65</td>
<td>0.60</td>
</tr>
<tr>
<td>Paco2</td>
<td>-0.67</td>
<td>-0.48</td>
</tr>
</tbody>
</table>
| HAI: hypopnoea/apnoea index. For further abbreviations see legends to table 1 and 2.

Discussion

Despite the low incidence of morbid obesity in Chinese patients, OSAS definitely occurs in this population [20]. Much evidence has suggested that disorders of ventilatory drive, in addition to obesity per se, are necessary to explain hypoventilation in hypercapnic OSAS [5, 6]. Patients with hypercapnia and/or hypoxaemia tend to have reduced ventilatory response to hypercapnic and hypoxic stimulation. Severe sleep hypercapnia will blunt the waking hypercapnic ventilatory response [21–23]. KUNITOMO et al. [24] demonstrated that the waking hypoxic ventilatory drive is inversely correlated with the magnitude of maximal oxygen desaturation during sleep, as well as the duration of oxygen desaturation as a percentage of total sleep time. Thus, it is possible that repetitive apnoea and exposure of the central chemoreceptors to hypercapnia causes adaptation and resetting of the ventilatory response to hypercapnia. Hypoxia may interfere with synthesis and turnover of a wide range of neurotransmitters [25–29]. In this study, the hypercapnic and hypoxic ventilatory drive were correlated with lowest Sao2, Paco2, and mean Sao2. Group I had a worse ventilatory response to hypercapnia and hypoxia and worse HAI, mean Sao2 and Paco2, than Group II.

In a large series of OSAS patients studied by KRIEGER et al. [30] hypercapnia was related to airway obstruction as well as to body weight. In order to control for this variable, we excluded all cases with FEV1/FVC <75%. Both LEECH et al. [31] and Guilleminault and Cummskey [12] have also reported series with no differences in FEV1/FVC between eucapnic and hypercapnic subjects.

Improvement of ventilatory response may reflect improvements in sleep efficiency, latency and architecture. Stoors and Dement [32] and Guilleminault and Rosekind [33] have shown that, in humans, sleep fragmentation alone worsens sleep apnoea and snoring. Whilst nasal CPAP did improve the sleep disturbance in our patients, there was no significant change in the time spent in REM sleep. This may have been due to technical reasons, such as first night effect on nasal CPAP, although Mahadevia et al. [34] has reported similar results, finding that the relative time spent in REM did not change significantly with CPAP.
those with very severe disease, which may account for the discrepancy in our findings. It is probably also more accurate to think of OSAS as falling along a spectrum of disease severity. Guilleminault's eucapnic patients with severe OSAS may have been very close to becoming chronically hypercapnic. At any rate, the varying responses suggest the need for further prospective studies with larger numbers of subjects.

In conclusion, hypercapnic OSAS patients with normal FEV1/FVC are more obese than eucapnic OSAS patients, have worse waking PaO2, and sleep oxygen desaturation, and have blunted ventilatory responses to both hypercapnia and hypoxia. Two weeks of effective nasal CPAP therapy may successfully correct both hypercapnic and hypoxic ventilatory response in these patients.

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References