Eur Respir J, 1994, 7, 2005–2010
DOI: 10.1183/09031936.94.07112005
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European Respiratory Journal
ISSN 0903 - 1936

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

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Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnoea syndrome. C-C. Lin. ©ERS Journals Ltd 1994.

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 ($P_{0.1}$) improved significantly after 2 weeks of nasal CPAP therapy in Group I, with normalization of arterial carbon dioxide tension ($Paco_2$) (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.

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Keywords: Hyponea/apnoea index, nasal CPAP, obstructive sleep apnoea syndrome, occlusion pressure, ventilatory drive

Received: June 28 1993
Accepted after revision August 28 1994

This study was supported by a grant from the National Science Council of the Republic of China (NSC 83 - 0412 - B - 195 - 005).

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 ($Paco_2$) 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 CO_2 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 $kg \cdot m^{-2}$), hypersomnolence on clinical evaluation, alveolar hypoventilation manifested by arterial hypoxaemia with carbon dioxide retention ($Paco_2 \geq 6$ 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) ≥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 >50, and lowest arterial oxygen saturation (Sa_{O_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 Sa_{O_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 α or θ electroencephalographic (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

	Group I			Group II		
	Before	After 2 weeks	After 1 month	Before	After 2 weeks	After 1 month
Age yrs	48±7	-	-	47±10	-	-
Sex M/F	5/1	-	-	21/3	-	-
Height cm	168±4	-	-	168±5	-	-
Body weight kg	111±9	-	108±8	96±7*	-	94±7
Body mass index $BW \cdot Ht^{-2}$	39.1±2.4	-	38.1±2.5	34.1±2.1*	-	33.6±2.2
Haemoglobin $g \cdot dl^{-1}$	17.4±0.5	-	15.0±0.6†	14.5±0.5*	-	14.2±0.4
Haematocrit %	56±0.6	-	44±0.6†	44±1.3*	-	44±1.2
FEV % pred	70±3.8	-	71±3.9	84±6.8*	-	83±6.6
FEV_1/FVC %	84±4.0	-	84±4.2	84±6.8	-	83±6.1
Pa_{O_2} kPa	10.0±0.7	12.1±0.7†	12.1±0.7†	11.9±0.7*	12.3±0.7	12.4±0.7
Pa_{CO_2} kPa	6.3±0.2	5.2±0.4†	5.4±0.4†	5.3±0.5*	5.3±0.5	5.2±0.5
pH	7.4±0.03	7.4±0.04	7.4±0.04	7.4±0.03	7.4±0.03	7.4±0.03
Baseline Sa_{O_2} %	93±0.5	95±0.5	95±0.5	96±0.5*	96±0.5	96±0.5
Mean Sa_{O_2} %	81±2.1	93±0.4†	94±0.4†	91±1.4*	94±0.4†	94±0.4†
Mean O_2 desaturation interval s	48±6	15±2†	14±2†	29±5*	8±2†	7±2†

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; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; Sa_{O_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 ($P_{0.1}$) [19] were regressed linearly against the end-tidal carbon dioxide tension (P_{CO_2}) values or fall in Sa_{O_2} from baseline (ΔSa_{O_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 Omheda 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 (Pa_{O_2}), Pa_{CO_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 Pa_{O_2}, baseline Sa_{O_2} and mean Sa_{O_2}, and a higher daytime Pa_{CO_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

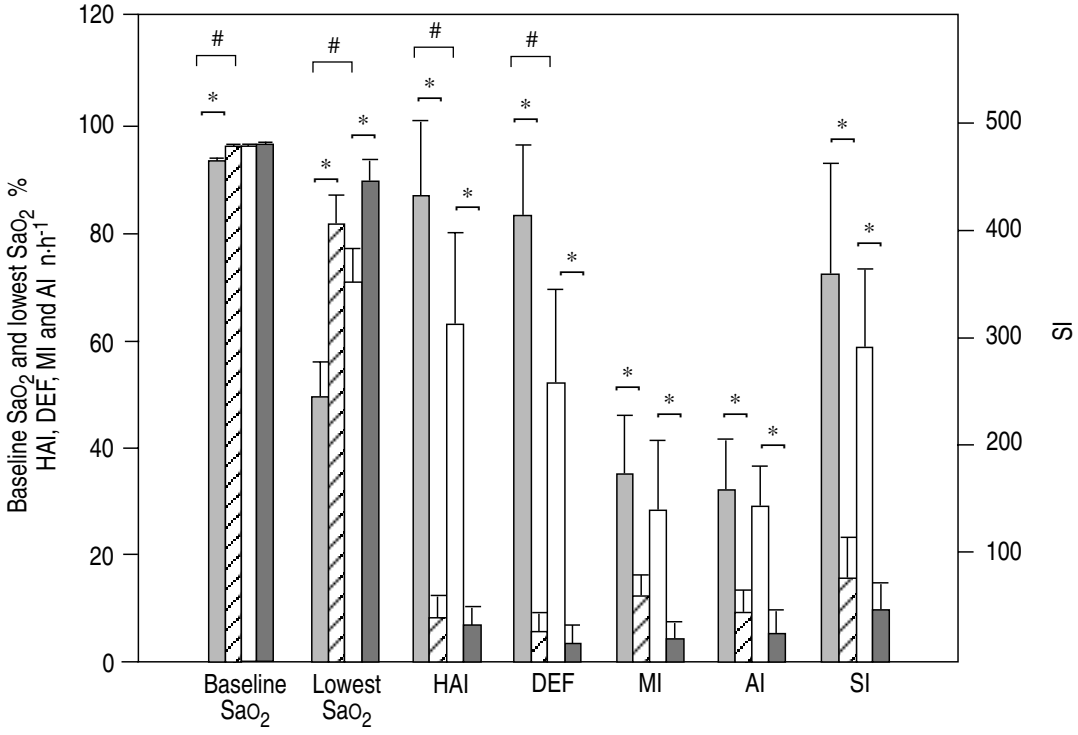

Fig. 1. – Comparison of baseline arterial oxygen saturation (Sa_{O_2}), lowest Sa_{O_2}, hypopnoea/apnoea index (HAI), desaturation event frequency (DEF), movement index (MI), arousal index (AI), and snore index (SI) between Group I and Group II, before and after nasal continuous positive airway pressure (CPAP) treatment (▨ : Group I before treatment; ▨ : Group I after treatment; □: Group II before treatment; ■ : Group II after treatment. There was significantly worse baseline Sa_{O_2}, lowest Sa_{O_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 Sa_{O_2} in Group I, and lowest Sa_{O_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 (*: $p<0.05$).

difference in mean O_2 desaturation interval between the two groups before nasal CPAP treatment. The Pao_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 Sao_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 Sao_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 Sao_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 Sao_2 (table 1), lowest Sao_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 V_E, $P_{0.1}$ 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 V_E, $P_{0.1}$ 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 Sao_2, lowest Sao_2, and $Paco_2$

The data correlation between ventilatory drive and $Paco_2$, HAI, and mean Sao_2 are listed in table 3. Both hypercapnic and hypoxic ventilatory drive are significantly correlated with lowest Sao_2, $Paco_2$ and mean Sao_2. Group I had a lower ventilatory response to hypercapnia and hypoxia (table 2), greater HAI, and lower mean Sao_2 and $Paco_2$ than Group II (fig. 1 and table 1).

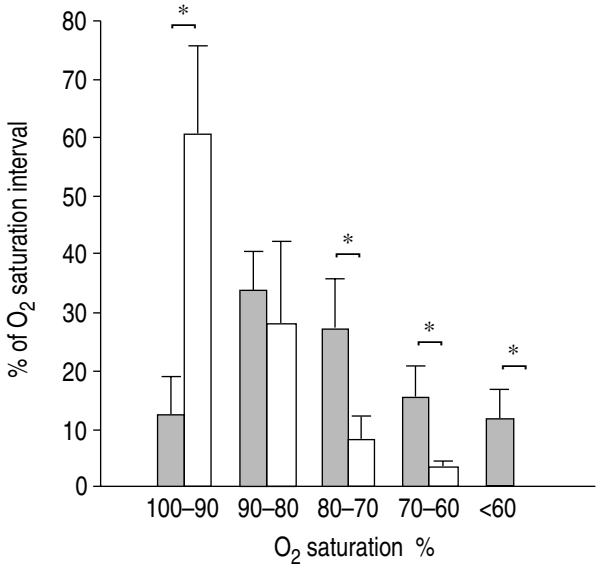

Fig. 2. – Comparison of percentage of O_2 saturation interval divided by total sleep time between Group I and Group II before nasal continuous positive airway pressure (CPAP) treatment. ▩ : Group I; □ : Group II. Group I spent a greater percentage of sleep time at lower oxygen saturation intervals during sleep. *: $p<0.05$, unpaired Student's t-test.

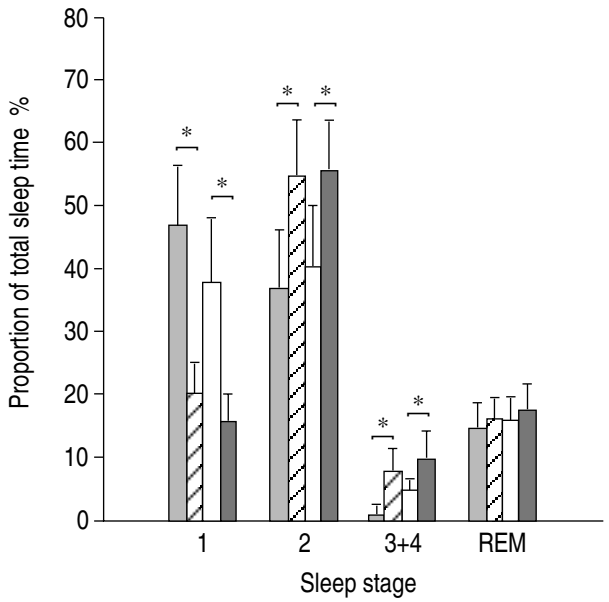

Fig. 3. – Comparison of the effect of nasal continuous positive airway pressure (CPAP) on sleep architecture. ▩ : Group I before treatment; ▨ : Group I after treatment; □ : Group II before treatment; ■ : Group II after treatment. Before nasal CPAP treatment, both groups spent a greater percentage of time in stage 1 sleep, with only a small percentage in stage 3+4. Treatment shortened stage 1 sleep but increased stage 2 and stage 3+4 sleep. Nasal CPAP did not change the percentage of time in rapid eye movement (REM) stage sleep. *: $p<0.05$, paired Student's t-test.

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

	Group I			Group II		
	Before	After 2 weeks	After 1 month	Before	After 2 weeks	After 1 month
Hypercapnic response						
Baseline V_E $l \cdot min^{-1}$	4.2±1.2	7.1±1.4†	7.9±1.6†	7.5±1.5*	7.5±1.6	7.3±1.5
$\Delta V_E/\Delta Pa_{CO_2}$ $l \cdot min^{-1}$ kPa	0.46±0.20	2.46±0.51†	2.5±0.48†	2.59±0.54	2.78±0.54	2.74±0.50
Baseline $P_{0.1}$ cmH_2O	0.4±0.2	0.9±0.2†	0.9±0.2†	0.8±0.2*	0.9±0.3	1.0±0.3
$\Delta P_{0.1}/\Delta Pa_{CO_2}$ cmH_2O/kPa	0.05±0.02	0.28±0.11†	0.30±0.12†	0.31±0.13*	0.33±0.12	0.34±0.12
Hypoxic response						
Baseline V_E $l \cdot min^{-1}$	4.5±1.4	6.9±0.11†	7.2±1.5†	7.3±1.3*	7.6±1.5	7.4±1.5
$\Delta V_E/\Delta Sa_{O_2}$ $l \cdot min^{-1}/\%Sa_{O_2}$	-1.49±0.45	-2.81±0.86†	-2.89±0.88†	-2.97±0.92*	-3.11±1.13	-3.02±1.08
Baseline $P_{0.1}$ cmH_2O	0.4±0.2	0.9±0.2†	0.9±0.2†	0.8±0.2*	0.9±0.3	1.0±0.3
$\Delta P_{0.1}/\Delta Sa_{O_2}$ $cmH_2O/\%Sa_{O_2}$	-0.08±0.03	-0.25±0.07†	-0.27±0.08†	-0.29±0.09*	-0.30±0.09	-0.32±0.09

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; V_E: minute ventilation; $P_{0.1}$: mouth occlusion pressure; Δ: difference. For further abbreviations see legend to table 1.

Table 3. – Simple correlation coefficients of HAI, mean Sa_{O_2}, Pa_{CO_2} and hypercapnic and hypoxic ventilatory response

	Hypercapnic response		Hypoxic response	
	$\Delta V_E/\Delta Pa_{CO_2}$	$\Delta P_{0.1}/\Delta Pa_{CO_2}$	$\Delta V_E/\Delta Sa_{O_2}$	$\Delta P_{0.1}/\Delta Sa_{O_2}$
HAI	-0.42	-0.29	0.58	0.45
Mean Sa_{O_2}	0.50	0.47	-0.61	-0.53
Lowest Sa_{O_2}	0.65	0.60	-0.63	-0.63
Pa_{CO_2}	-0.67	-0.48	0.56	0.65

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 Sa_{O_2}, Pa_{CO_2} and mean Sa_{O_2}. Group I had a worse ventilatory response to hypercapnia and hypoxia and worse HAI, mean Sa_{O_2} and Pa_{CO_2}, 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 FEV_1/FVC <75%. Both LEECH *et al*. [31] and GUILLEMINAULT and CUMMISKEY [12] have also reported series with no differences in FEV_1/FVC between eucapnic and hypercapnic subjects.

Improvement of ventilatory response may reflect improvements in sleep efficiency, latency and architecture. STOOHS 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 hypoventilation 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 CO_2 in hypercapnic OSAS patients. In our hypercapnic OSAS patients, both slope and baseline shifted toward normal in response to both hypoxia and hypercapnia. This discrepancy may be due to different criteria for patient selection and/or the fact that hypercapnic OSAS patient are heterogeneous.

Our eucapnic OSAS patients did not have abnormal baseline ventilatory responses, in contrast to subjects with severe eucapnic OSAS described by GUILLEMINAULT and CUMMISKEY and AUBERT-TULKENS *et al*. [11]. Guilleminault's group had only a small number of subjects, limited to

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 FEV_1/FVC are more obese than eucapnic OSAS patients, have worse waking Pa_{O_2} 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.

***Acknowledgement*:** M.J. Buttrey corrected the English of the manuscript.

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