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Sleep hypoventilation in hypercapnic chronic obstructive pulmonary disease: prevalence and associated factors

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ABSTRACT: Sleep hypoventilation (SH) may be important in the development of hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD). The prevalence of SH, associated factors, and overnight changes in waking arterial blood gases (ABG), were assessed in 54 stable hypercapnic COPD patients without concomitant sleep apnoea or morbid obesity.

Lung function assessment, anthropomorphic measurements, and polysomnography with ABG measurement before and after sleep were conducted in all patients. Transcutaneous carbon dioxide tension (P_{t,CO_2}) was measured in sleep, using simultaneous arterial carbon dioxide tension (P_{a,CO_2}) for *in vivo* calibration and to correct for drift in the sensor.

Of the patients, 43% spent $\geqslant$20% of sleep time with P_{t,CO_2} >1.33 kPa (10 mmHg) above waking baseline. Severity of SH was best predicted by a combination of baseline P_{a,CO_2}, body mass index and per cent rapid-eye movement (REM) sleep. REM-related hypoventilation correlated significantly with severity of inspiratory flow limitation in REM, and with apnoea/hypopnoea index. P_{a,CO_2} increased mean±SD 0.70±0.65 kPa (5.29±4.92 mmHg) from night to morning, and this change was highly significant. The change in P_{a,CO_2} was strongly correlated with severity of SH.

Sleep hypoventilation is common in hypercapnic chronic obstructive pulmonary disease, and related to baseline arterial carbon dioxide tension, body mass index and indices of upper airway obstruction. Sleep hypoventilation is associated with significant increases in arterial carbon dioxide tension night-to-morning, and may contribute to long-term elevations in arterial carbon dioxide tension.

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and is now the fourth-leading cause of death in the USA [1]. Chronic hypercapnia is known to be a poor prognostic factor in COPD [2] but the causes of hypercapnia are not completely understood [3]. Patients with severe COPD are known to be at risk of sleep hypoventilation (SH) [4] and it has been proposed that SH may play a role in the pathogenesis of chronic hypercapnia through blunting of central chemoreceptor responses to carbon dioxide (CO_2), secondary to gradual renal HCO_3^- retention [3, 5]. In support of this hypothesis are the results from a trial of nocturnal noninvasive ventilation (NIV) in COPD, which showed improvements in awake arterial carbon dioxide tension (P_{a,CO_2}) [6]. P_{a,CO_2} correlated solely with reductions in transcutaneous carbon dioxide tension (P_{t,CO_2}) during sleep.

Despite its potential importance for prognosis, no study has investigated the prevalence of SH in hypercapnic COPD. However, it is known that transient oxygen desaturation is common in severe COPD [7], and particularly in hypercapnic COPD [8]. This phenomenon is at least partly due to hypoventilation, but there may also be a contribution from altered ventilation/perfusion (V'/Q') relationships [7, 9]. The mechanisms of SH in hypercapnic COPD are also uncertain. A fall in central respiratory drive, particularly in rapid-eye movement (REM) sleep, is likely to be important [7] but there may also be a significant contribution from increased upper airways resistance. "Overlap syndrome", the combination of COPD and obstructive sleep apnoea/hypopnoea syndrome (OSAH), is said to predispose to daytime hypercapnia and hypoxaemia independently of lung function [10]. However, the role of the upper airway in SH in COPD patients without overt OSAH has received little attention. An increase in upper airways resistance at sleep onset may contribute to the fall in ventilation during sleep in normal subjects [11]. It is therefore possible that patients whose respiratory muscles are working close to their endurance limits [12] cannot compensate for the extra load imposed by the upper airway during sleep.

The present study was conducted in order to address some of these questions. To do this the baseline data for the first 80 patients enrolled in the Australian trial of Noninvasive Ventilation in Chronic Airflow Limitation (AVCAL) was analysed. AVCAL is a multicentre, randomised, controlled trial of chronic domiciliary NIV in stable hypercapnic COPD.

Recruitment commenced in 1998. There were three main aims of the present study: 1) to document the prevalence of SH in stable hypercapnic COPD; 2) to determine which factors are associated with SH in this population with the specific hypothesis that factors linked with increased upper airways resistance during sleep (obesity, alcohol consumption, snoring and inspiratory flow limitation in sleep) would worsen hypoventilation; and 3) to determine if awake P_{a,CO_2} is higher in the morning than in the evening in these subjects, and if the night-to-morning change in P_{a,CO_2} correlates with severity of SH.

Materials and methods

Patients

All patients were undergoing baseline assessment in Adelaide, Melbourne or Sydney, Australia, for the AVCAL trial. All respiratory physicians in these three centres were contacted directly to inform them of the trial aims and design. They were provided with inclusion and exclusion criteria and requested to refer all patients they considered appropriate for assessment. Advertisements were also placed in newsletters of the Royal Australasian College of Physicians, the Thoracic Society of Australia and New Zealand and the Australasian Sleep Association.

The inclusion criteria were: 1) a clinical history consistent with stable COPD without an exacerbation of airways disease for at least 4 weeks at the time of evaluation; 2) irreversible airflow obstruction (forced expiratory volume in one second (FEV1) <1.5 L or <50% predicted, FEV1/forced vital capacity <65%, ΔFEV1 with bronchodilator <15%, or if FEV1 <1.5 L, ΔFEV1 <200 mL); 3) daytime awake P_{a,CO_2} >6.12 kPa (46 mmHg) while in a stable condition; and 4) on oxygen therapy for a minimum of 3 months with a prescription meeting American Thoracic Society guidelines.

The exclusion criteria were: 1) morbid obesity (body mass index (BMI) $\geqslant$40); 2) significant OSAH (apnoea/hypopnoea index (AHI) $\geqslant 20 \cdot h^{-1}$ (see scoring criteria below)); 3) previous treatment with domiciliary NIV; and 4) age $\geqslant$80 yrs.

The protocol was approved by the Research and Ethics Committees of all participating institutions. All participants gave informed written consent.

Measurements

Height and weight were measured and BMI calculated. Spirometry pre- and postbronchodilator, lung volumes and single-breath diffusion capacity of the lung for carbon monoxide were recorded. Arterial blood was drawn for blood-gas analysis while on the prescribed flow of oxygen, and after breathing room air for 15 min, if tolerated.

Full-attended polysomnography was performed (Compumedics S series, Abbotsford, Victoria, Australia) while on prescribed oxygen flow delivered by nasal cannulae. Measured parameters were electroencephalography (EEG), left and right electro-oculography, submental electromyography, airflow (by thermistor and/or by nasal pressure cannula), thoracoabdominal movement by inductance bands, leg movements, body position, and arterial oxygen saturation.

P_{t,CO_2} was recorded in all subjects with the TINA TCM 3 device (Radiometer, Copenhagen, Denmark) calibrated according to the manufacturers instructions. Arterial blood gases (ABG) were measured in the evening prior to sleep and again in the morning at least 5 min after final awakening, on an identical flow of oxygen while supine. Wakefulness was confirmed on the EEG. The simultaneous stable P_{t,CO_2} value at the time of each blood gas sample was noted.

A detailed history of lifetime alcohol consumption was taken using the "timeline followback" technique [13]. This involves aiding patients' memories of their past alcohol intake by using key events in their lives, *e.g.* first job, armed forces service, marriage, divorce, retirement, death of spouse *etc.* The technique has been validated previously and gives highly reproducible results [13, 14]. The information was used to calculate lifetime alcohol consumption and current consumption.

Data processing

Sleep was manually staged in 30-s epochs according to standard criteria [15]. Apnoea was defined as a complete cessation of airflow for 10 s. Hypopnoea was defined as a >50% reduction in amplitude in two of the following for >10 s: airflow, thoracic and abdominal respiband signals. Because all patients were on supplemental oxygen, no desaturation criterion was used in scoring hypopnoeas. For this reason, a rather high AHI cut-off ($\geqslant 20 \cdot h^{-1}$) was used in eliminating subjects with OSAH. In the Sleep Heart Health Study cohort, it was found that omitting desaturation from the criteria for scoring respiratory events produced up to a 10-fold increase in median AHI [16].

Night-to-morning $\Delta P_{a,CO_2}$ were calculated. P_{t,CO_2} data were sampled at 1 Hz and mean P_{t,CO_2} values calculated for each epoch of sleep. Evening P_{a,CO_2} was used as an *in vivo* calibration (fig. 1) to adjust for baseline offset in P_{t,CO_2} measurements.

Simultaneous P_{t,CO_2} and P_{a,CO_2} results were examined before and after sleep. If the P_{t,CO_2} minus P_{a,CO_2} had changed across the night, this change was attributed to P_{t,CO_2} sensor drift. The morning P_{t,CO_2} value was corrected for this drift, and all P_{t,CO_2} values in between were corrected using linear interpolation (fig. 1).

SH was defined as >20% of total sleep time (TST) spent with "corrected" P_{t,CO_2} >1.33 kPa (10 mmHg) above supine waking baseline levels. Severity of SH was assessed in each subject in three ways: 1) the increment in P_{t,CO_2} (wakefulness–sleep) above which 20% of TST was spent (20%incr; fig. 2); 2) the maximal increment of P_{t,CO_2} (maxincr; fig. 2); and 3) REM-related hypoventilation, measured as the mean rise in P_{t,CO_2} from the average in the preceding 5 min of nonrapid-eye movement (NREM) sleep to the maximum in each period of REM (ΔNREM–REM). This value is less likely to be influenced by drift in the P_{t,CO_2} sensor as the change is calculated over a much shorter time period, usually <15 min.

If a drift of <1.33 kPa (10 mmHg) was seen from night-to-morning in the P_{t,CO_2} sensor, or if evening and morning P_{a,CO_2} were not available to validate P_{t,CO_2}, the 20%incr and the maxincr values were excluded from analysis but the ΔNREM–REM values were retained.

Stable sleep was defined as an epoch without a stage change in the previous four epochs. A random sample of 10 nonconsecutive epochs of stable sleep in each stage was chosen by computer in each of the 54 patients in whom nasal pressure was measured. Each breath was visually scored for the presence of inspiratory flow limitation, without reference to the SH or blood-gas data for that subject, by a physician experienced in evaluation of inspiratory flow limitation from clinical data. Breaths were scaled to be of approximately uniform duration and amplitude. Evaluation was made purely on the basis of the shape of the inspiratory nasal pressure trace [17]. Breaths were assigned a score of 0, 1 or 2 corresponding to no flow limitation, mildly flow-limited, or

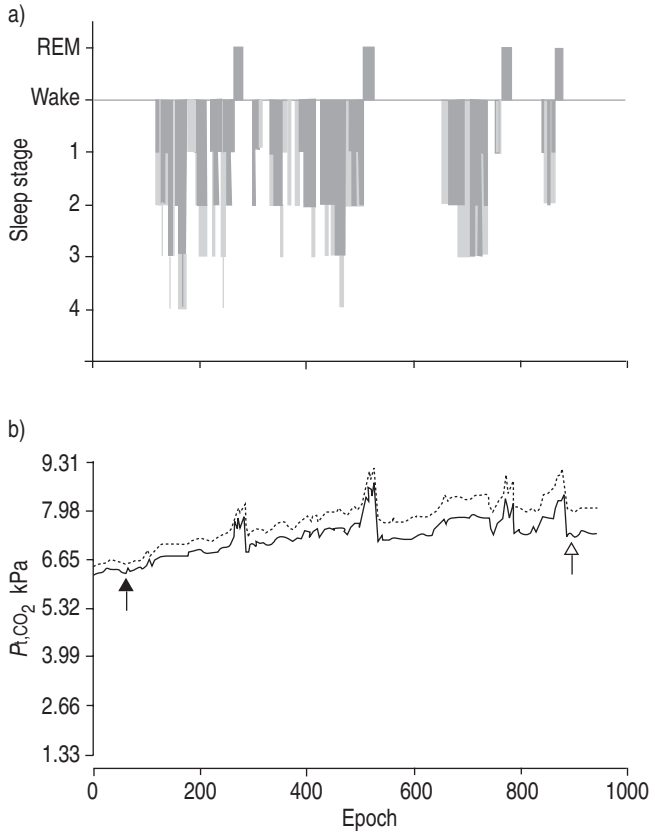

Fig. 1. – a) Sample hypnogram and b) transcutaneous carbon dioxide tension (P_{t,CO_2}) record illustrating P_{t,CO_2} corrections. The evening arterial carbon dioxide tension (P_{a,CO_2}) sample was used as an *in vivo* calibration and the morning P_{a,CO_2} to correct for P_{t,CO_2} sensor drift. Closed arrow indicates epoch 55 (P_{t,CO_2} 6.61 kPa (49.7 mmHg), P_{a,CO_2} 6.29 kPa (47.3 mmHg)); Open arrow indicates epoch 923 (P_{t,CO_2} 8.09 kPa (60.8 mmHg), P_{a,CO_2} 7.39 kPa (55.6 mmHg)). REM: rapid-eye movement. ——: corrected P_{t,CO_2}; ·····: uncorrected P_{t,CO_2}.

markedly flow-limited. A mean score per breath was derived for each stage of NREM sleep. These were then weighted according to the percentage of total NREM sleep occupied by that stage, and a weighted mean for all of NREM sleep was calculated. A separate mean score per breath was calculated for REM (REMflow). A blind rescoring in a random sample of 65 epochs produced a concordance of 87%.

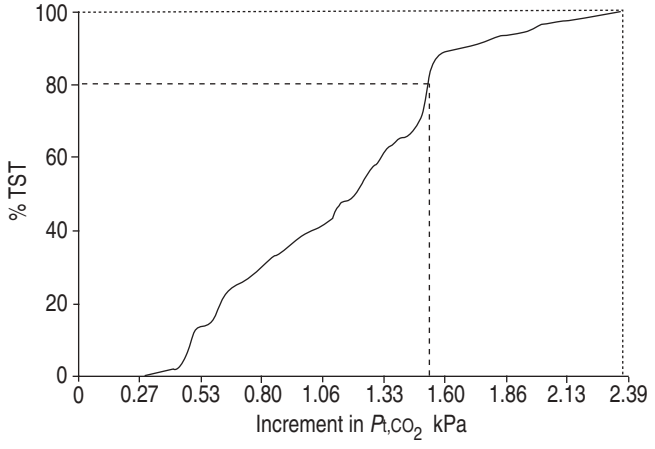

Fig. 2. – Cumulative frequency of transcutaneous carbon dioxide tension (P_{t,CO_2}) values expressed as the increment in P_{t,CO_2} over waking baseline, with time expressed as percentage total sleep time (% TST), for the same patient as in fig. 1. – – –: P_{t,CO_2} increment above which 20% of TST was spent (1.53 kPa (11.5 mmHg)); ·····: maximum increment in P_{t,CO_2} (2.37 kPa (17.84 mmHg)).

Statistics

The correlations between lung function and blood-gas parameters, as well as reported alcohol consumption, indices of inspiratory flow limitation and polysomnographic variables with measures of SH were assessed using Pearson′s product moment with Spearman′s rho for non-normally distributed variables. Predictive power of combinations of variables was assessed using forward stepwise-linear regression, with criteria for entry into the model being a probability of F of <0.05 and for removal a probability of >0.1. Comparison of evening and morning ABG measurements was performed using paired t-tests. Results are given as mean±SD unless otherwise stated.

Results

Baseline data from the first 80 patients (54 male, 26 female) enrolled in the AVCAL trial were analysed. Evening and morning blood-gas samples were taken from 67 patients under satisfactory conditions as defined above. There was no systematic overestimation of $\Delta P_{a,CO_2}$ by P_{t,CO_2} as $\Delta P_{a,CO_2}$ increased (fig. 3).

Amongst these 67, data on P_{t,CO_2} trends across the night were excluded from analysis in 13 because of excessive drift of the P_{t,CO_2} sensor (11 patients), very high P_{t,CO_2} values that were outside the range of the recording equipment (one patient) and failure to record P_{t,CO_2} value at the time of ABG (one patient). Data on overnight trends in P_{t,CO_2} were analysed in the remaining 54 patients. Their ages, baseline lung function and ABG, BMI and polysomnographic variables are shown in table 1. There was no significant difference in any of the parameters in table 1 between the excluded patients and those in whom SH data was retained. In these 54 subjects the mean

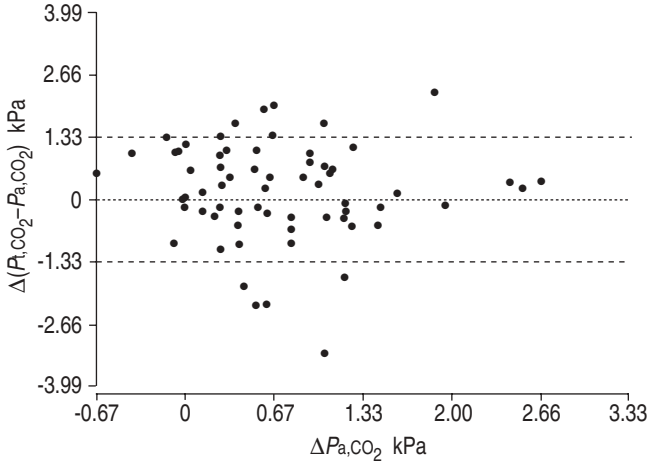

Fig. 3. – Error in measurement of change in arterial carbon dioxide tension (P_{a,CO_2}) night-to-morning by transcutaneous carbon dioxide tension (P_{t,CO_2}). There was no relationship between (P_{t,CO_2}–P_{a,CO_2}) and $\Delta P_{a,CO_2}$, indicating there was no systematic overestimation of changes in P_{a,CO_2} by P_{t,CO_2}. Therefore, changes in (P_{t,CO_2}–P_{a,CO_2}) were assumed to be due to drift in the P_{t,CO_2} sensor. Data from subjects in whom P_{t,CO_2} measurements demonstrated drift of >1.33 kPa (10 mmHg) were excluded from analysis. In the remaining 54 subjects, drift in the P_{t,CO_2} sensor was corrected for, as in figure 1.

Table 1. – Baseline characteristics

Characteristics	
Subjects n	54
Age yrs	68.4±8.0
BMI kg·m^{-2}	25.3±5.5
FEV1 % pred	24.8±8.1
FEV1/FVC %	33.1±10.0
TLC % pred	116.5±23.5
RV/TLC %	66.9±8.2
Room air P_{a,O_2} kPa	6.98±2.57
Room air P_{a,CO_2} kPa	7.26±1.06
Room air pH	7.40±0.03
AHI events·h sleep^{-1}	4.9±5.1
Arousal index arousals·h sleep^{-1}	16.4±8.7
Sleep efficiency	57.4±16.0

Data are presented as mean±SD unless otherwise stated. BMI: body mass index; FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; AHI: apnoea/hypopnoea index; Sleep efficiency: (total sleep time/time available for sleep)×100.

drift in the sensor across the night was 0.21±0.65 kPa (1.6± 4.9 mmHg). Figure 4 is a frequency histogram of the 20%incr values. Of these 54 subjects, 23 or 43% were found to have SH according to the authors' *a priori* definition.

Tables 2 and 3 give univariate correlation coefficients between measures of SH and putative associated factors. Multiple linear-regression analysis produced the following equations:

$$20\%_{incr} = 0.40P_{a,CO_2} + 0.34BMI + 0.29\%REM - 25.4\,(R^2 = 0.35) \quad (1)$$

$$Max_{incr} = 0.52P_{a,CO_2} + 0.54BMI + 0.39\%REM - 32.9\,(R^2 = 0.48) \quad (2)$$

$$\Delta NREM - REM = 0.13REM_{flow} + 0.0028\%SWS + 0.63\,(R^2 = 0.19) \quad (3)$$

where SWS is slow-wave sleep.

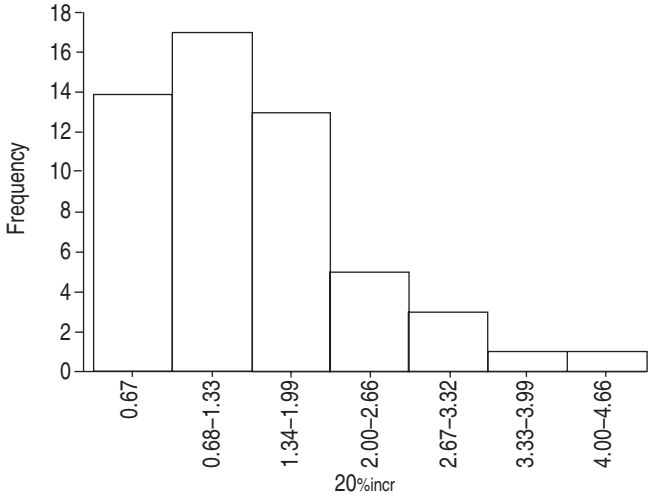

Fig. 4. – Histogram of the range of severity of sleep hypoventilation (n=54). 20%incr: increment in transcutaneous carbon dioxide tension above supine waking baseline, above which 20% of total sleep time was spent. Subjects with 20%incr >1.33 kPa (10 mmHg) were considered to demonstrate sleep hypoventilation (23 subjects).

Morning ABG samples were taken 33.5±30 min after final wakening. Table 4 gives mean values for evening and morning P_{a,CO_2}, pH and H^+ concentration. P_{a,CO_2} rose by 0.70±0.65 kPa

Table 2. – Univariate correlation coefficients for measures of overnight sleep hypoventilation

	20%incr	Maxincr
Age	-0.19 (0.17)	-0.05 (0.72)
Female#	-0.15 (0.27)	-0.10 (0.50)
BMI	0.27 (0.05)	0.37 (0.01)
FEV1 % pred#	0.19 (0.17)	0.19 (0.19)
FVC % pred	0.05 (0.72)	-0.06 (0.71)
FEV1/FVC	0.10 (0.46)	0.25 (0.08)
P_{a,O_2}	-0.18 (0.24)	-0.18 (0.26)
P_{a,CO_2}	0.39 (0.009)	0.42 (0.007)
Life alcohol#	-0.29 (0.06)	-0.11 (0.52)
Current alcohol#	-0.31 (0.04)	-0.23 (0.14)
AHI#	0.13 (0.33)	0.22 (0.13)
%SWS	-0.10 (0.46)	-0.05 (0.75)
%REM	0.28 (0.04)	0.32 (0.03)
TST	0.18 (0.19)	0.17 (0.25)
REMflow	0.12 (0.53)	0.17 (0.37)
NREMflow	0.00 (0.98)	0.16 (0.38)

Data are presented as univariate correlation coefficients (p-values). 20%incr: increment in transcutaneous carbon dioxide tension (P_{t,CO_2}) from wakefulness above which 20% of total sleep time (TST) was spent; Maxincr: maximum increment in P_{t,CO_2} over wakefulness; BMI: body mass index; FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; Life alcohol: lifetime alcohol consumption; Current alcohol: current alcohol consumption; AHI: apnoea/hypopnoea index; %SWS: percentage TST in slow-wave sleep; %REM: percentage TST in rapid-eye movement (REM) sleep; REMflow: mean score per breath for inspiratory flow limitation in REM sleep; NREMflow: mean score per breath for inspiratory flow limitation in non-REM sleep. #: non-normally distributed variable.

Table 3. – Univariate correlation coefficients for sleep hypoventilation in rapid-eye movement (REM) sleep

	ΔNREM–REM
Age	-0.13 (0.29)
Female#	-0.03 (0.78)
BMI	0.09 (0.45)
FEV1 % pred#	0.04 (0.75)
FVC % pred	-0.29 (0.02)
FEV1/FVC	0.20 (0.1)
P_{a,O_2}	-0.02 (0.85)
P_{a,CO_2}	0.18 (0.17)
Life alcohol#	0.02 (0.88)
Current alcohol#	-0.08 (0.55)
AHI#	0.25 (0.04)
AHI in REM sleep#	0.24 (0.05)
%REM	-0.12 (0.32)
%SWS	0.32 (0.01)
REMflow	0.31 (0.04)
NREMflow	0.05 (0.71)

Data are presented as univariate correlation coefficients (p-values). ΔNREM–REM: change in transcutaneous carbon dioxide tension on entry to REM from nonrapid-eye movement (NREM) sleep; BMI: body mass index; FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; Life alcohol: lifetime alcohol consumption; Current alcohol: current alcohol consumption; AHI: apnoea/hypopnoea index; %REM: percentage total sleep time (TST) in REM sleep; %SWS: percentage TST in slow-wave sleep; REMflow: mean score per breath for inspiratory flow limitation in REM sleep; NREMflow: mean score per breath for inspiratory flow limitation in non-REM sleep. #: non-normally distributed variable.

Table 4. – Night-to-morning changes in blood gas parameters

	Night	Morning	Change
P_{a,CO_2} kPa	7.86±1.37	8.57±1.65	0.70±0.65***
pH	7.38±0.04	7.35±0.05	-0.03±0.03***
H^+ concentration mmol·L^{-1}	42.3±4.0	45.1±4.9	2.8±3.2***

Data are presented as mean±SD. ***: p<0.001.

Table 5. – Univariate correlation coefficients for night-to-morning changes in awake arterial carbon dioxide tension (P_{a,CO_2})

	$\Delta P_{a,CO_2}$
Age	-0.35 (0.003)
Female#	0.28 (0.02)
BMI	0.27 (0.03)
20%incr	0.78 (<0.001)
Maxincr	0.69 (<0.001)
ΔNREM–REM	0.28 (0.04)
P_{a,CO_2}	0.42 (0.002)
P_{a,O_2}	-0.28 (0.04)
pH	-0.25 (0.07)
FEV1 % pred	-0.04 (0.75)
FEV1/FVC	0.02 (0.84)
RV/TLC#	-0.12 (0.34)
AHI#	0.02 (0.89)
%REM	0.16 (0.20)
REMflow	0.03 (0.83)
NREMflow	0.06 (0.70)
Current alcohol#	-0.27 (0.04)
Life alcohol#	-0.34 (0.01)

Data are presented as univariate correlation coefficients (p-values). BMI: body mass index; 20%incr: increment in transcutaneous carbon dioxide tension (P_{t,CO_2}) from wakefulness above which 20% of total sleep time (TST) was spent; Maxincr: maximum increment in P_{t,CO_2} over wakefulness; ΔNREM–REM: change in transcutaneous carbon dioxide tension on entry to rapid-eye movement (REM) sleep from nonrapid-eye movement (NREM) sleep; P_{a,O_2}: arterial oxygen tension; FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; AHI: apnoea/hypopnoea index; %REM: percentage TST in REM sleep; REMflow: mean score per breath for inspiratory flow limitation in REM sleep; NREMflow: mean score per breath for inspiratory flow limitation in non-REM sleep; Current alcohol: current alcohol consumption; Life alcohol: lifetime alcohol consumption. #: non-normally distributed variable.

(5.29±4.92 mmHg) across the night (p<0.001). Night-to-morning $\Delta P_{a,CO_2}$ correlated with all measures of SH (table 5).

Multiple regression analysis produced the following equation:

$$\Delta P_{a,CO_2} = 0.5320\%\text{incr} - 0.13\text{age} + 8.8\ (R^2 = 0.66) \qquad (4)$$

Discussion

This study has shown that SH is common in hypercapnic COPD, occurring in 43% of the population. Severity of SH correlated with daytime P_{a,CO_2} and with BMI, and during REM with severity of inspiratory flow limitation and with AHI. In contrast to earlier reports in normal subjects [18, 19], the authors found a significant increase in waking carbon dioxide tension (PCO_2) between night and morning in these hypercapnic COPD patients. The night-to-morning rise in P_{a,CO_2} was highly correlated with severity of SH. This is the first study to document the prevalence of SH in hypercapnic COPD. A number of studies have examined the prevalence of REM-related oxygen desaturation in sleep in COPD [8, 20, 21]. However these desaturations may be partially due to V'/Q' disturbance [7, 9]. One previous study measured P_{t,CO_2} during sleep in 23 COPD patients and 33 normal controls [22]. Mean maximal increase in P_{t,CO_2} was 0.80 kPa (6 mmHg) in the COPD patients and was not different to the controls. These results differ from those in the current study, probably because few of the patients in the study by MIDGREN and HANSSON [22] were hypercapnic (P_{a,CO_2} 5.59±0.80 kPa (42±6 mmHg)). In the present study, there was a strong correlation in the subjects between daytime P_{a,CO_2} and severity of SH. Previously, hypercapnia has been shown to be a risk factor for REM-related desaturation in COPD [8, 21, 23].

OSAH appears be an important cause of hypercapnia in some patient groups [10, 14, 24]. Continuous positive airways pressure has been shown to restore eucapnia and increase ventilatory response to CO_2 in morbidly obese hypercapnic patients with OSAH [24]. Hypercapnia that appears disproportionate to level of lung function impairment has been associated with the presence of obstructive sleep apnoea (OSA) in COPD patients [10]. CHAN *et al.* [14] showed that hypercapnic COPD patients had many more sleep-disordered breathing events, had higher BMIs and smaller upper airway cross-sectional areas than eucapnic controls matched for lung function.

In the current study, the hypothesis that lesser degrees of upper airways obstruction, other than OSAH, could contribute to sleep hypoventilation in severe COPD was addressed. Even after exclusion of patients with OSAH, severity of inspiratory flow limitation in REM, and AHI in both REM and NREM sleep were found to be predictive of REM-related hypoventilation. BMI was significantly correlated with SH across the whole night.

A surprising finding was an inverse correlation with alcohol consumption. This negative correlation seems counter-intuitive given what is known about the acute effects of alcohol in sleep, especially in males [25, 26]. These findings could not be explained by a reduction in REM sleep due to chronic alcohol abuse. It is possible that heavy drinkers who were susceptible to the effects of alcohol on sleep-disordered breathing were excluded from the study due to a diagnosis of OSAH, leaving a "survivor population" who either drank minimal alcohol or were not susceptible to sleep-disordered breathing. Ultimately, the authors do not have a definite explanation for this finding, which may be due to chance.

Another interesting result was the finding that %SWS was an independent predictor of NREM-to-REM change in P_{t,CO_2}. This may also be a chance finding but may relate to the fact that the upper airway is more stable in SWS than in lighter NREM stages; in REM it is at its most vulnerable to collapse [27]. Therefore the transition from SWS to REM would be more likely to produce the greatest change in ventilation.

Daytime P_{a,CO_2} was the factor most strongly associated with both 20%incr and maxincr. This is consistent with a number of studies that have shown daytime hypercapnia and awake ventilatory response to CO_2 correlated with propensity to REM-related desaturation in COPD [8, 20, 23]. Correlations cannot prove causation, and even if the factors are causally related, they do not establish direction of causation. It is possible that worsening daytime hypercapnia is the result, not the cause of SH. The largest study of predictors of hypercapnia in COPD included BMI in the final regression equation for CO_2 [28]. While obesity may influence daytime P_{a,CO_2} *via* mass loading of the chest wall, both in wakefulness and sleep, it may also increase upper airway resistance in sleep, worsening SH and blunting chemosensitivity.

The authors found that P_{a,CO_2} remained elevated over evening levels 33.5±30 min after final wakening. They believe

this is the first report of such a change in the literature. This contrasts with normal subjects who show no difference in $P\mathrm{CO}_2$ before and after sleep [18, 19]. $\Delta P\mathrm{a,CO}_2$ was highly correlated with severity of SH (table 3) and the combination of 20%incr and age explained 66% of the variance. The authors believe this provides supporting evidence for the theory that nocturnal hypoventilation can influence daytime $P\mathrm{a,CO}_2$ in severe COPD.

It has been proposed that SH contributes to development of chronic hypercapnia in COPD through the mechanism of gradual renal HCO_3^- retention. Night-to-morning changes in HCO_3^- observed in the present population were compared with the change predicted for acute on chronic hypercapnia in published equations [29], but the authors were unable to demonstrate any renal HCO_3^- retention across the night due to SH. Therefore, if little or no renal compensation occurred, why did these patients not return to their presleep ventilatory status on wakening? There are a number of possible explanations for this. First, renal HCO_3^- retention may have occurred in the subjects but was too small to be detected because of the wide confidence intervals of the predicted response [29]. Second, compensation may have occurred in the cerebrospinal fluid overnight. With the fall in $P\mathrm{a,CO}_2$ on awakening, the cerebrospinal fluid would become relatively alkalotic, increasing pH in the environment of the medullary chemoreceptors and so reducing respiratory drive. A third possible explanation for the results is that acute hypercapnia has significant negative effects on the ability of the respiratory muscles to generate force and predisposes them to fatigue [30]. Therefore, it may be that despite similar respiratory centre output, the mechanical response of the muscles is temporarily impaired in the first few hours after waking in patients with significant SH. Finally, there may be a contribution from the normal circadian rhythms of hypercapnic ventilatory response and end-tidal CO_2 [31].

Methodological considerations

Study population. As with all clinical trials the study population consisted only of those subjects who were both referred for assessment and consented to be enrolled in the AVCAL trial. This process always includes some referral bias. However, the authors attempted to avoid studying a population only referred for sleep assessment as much as possible.

Patients who were morbidly obese (BMI $\geqslant$40) were excluded and the mean BMI of the study population was 25.7 ± 5.7 kg·m^{-2}. In addition patients with concomitant OSA were excluded. Mean AHI of the study population was 4.7 ± 5.0. The lowest quartile of median AHI scores in the 5,046 participants in the Sleep Heart Health Study [16] had an AHI up to 18.3 when no desaturation criterion was included in the definition of hypopnoea, compared with the lowest quartile of up to AHI 3.7, when using a definition also requiring 3% desaturation. The authors believe therefore that using an AHI cut-off of 20 to exclude patients with OSA was justified.

From 80 patients studied, 26 were excluded for technical reasons. However, there was no difference in any of the baseline characteristics recorded between the excluded subjects and those whose data was retained. The authors believe that the group studied was truly representative of the general hypercapnic COPD population.

Use of supplemental oxygen. Supplemental oxygen may worsen hypercapnia during sleep in COPD [32]. Therefore, it is possible that SH would have been less severe if these patients had been studied without oxygen. However all subjects were studied on their usual prescribed oxygen flow. Therefore, the authors believe the data more truly represents SH in the clinical situation. In addition, they felt that if severe desaturation was seen, or if the patient became very dyspnoeic during the night it would have been ethically unacceptable to withhold oxygen from patients for whom it was part of their usual therapy. If oxygen were recommenced part way through the study this would have invalidated $P\mathrm{t,CO}_2$ and $P\mathrm{a,CO}_2$ measurements, as any changes could have been due to reintroduction of oxygen.

Transcutaneous carbon dioxide tension measurement. SH has been defined as an abnormal increase in $P\mathrm{a,CO}_2$ during sleep [4]. Diagnostic criteria proposed by this task force required an increase in $P\mathrm{a,CO}_2$ >1.33 kPa (10 mmHg) from awake supine values during sleep or oxygen desaturation during sleep not explained by apnoea or hypopnoea events.

For the reasons elaborated above, the authors felt they could not withhold oxygen from these patients during their polysomnographs. Furthermore, comparison of severity of hypoventilation using oxygen saturation is difficult when patients begin at different points on the oxyhaemoglobin desaturation curve. Finally, desaturation is a nonspecific finding, which may also be caused by change in lung or closing volume with deterioration in V'/Q' inequality [4, 7]. Therefore, oxygen saturation was not used as an index of SH.

Insertion of an indwelling arterial line to measure $P\mathrm{a,CO}_2$ could not be justified in this clinical trial and was likely to deter patients from enrolling. It is accepted that $P\mathrm{t,CO}_2$ is an imperfect measure of $P\mathrm{a,CO}_2$. There are many reasons for the differences in the two values when measured simultaneously [33] and commercial $P\mathrm{t,CO}_2$ monitors incorporate software to correct for some of these factors. A number of studies in adults have found high correlations with simultaneous $P\mathrm{a,CO}_2$ [33–35]. Control of sleep-related increases in $P\mathrm{t,CO}_2$ has also been found to be a predictor of improvement in daytime $P\mathrm{a,CO}_2$ with noninvasive positive-pressure ventilation in COPD [6]. Nevertheless, two studies in the setting of SH have found large discrepancies between $P\mathrm{t,CO}_2$ and simultaneously measured $P\mathrm{a,CO}_2$ [36, 37]. Neither of these studies used the approach of *in vivo* calibration of the device, though the study of ROSNER *et al.* [37] suggested accuracy and precision would be improved if this were performed. After *in vivo* calibration the question becomes whether $P\mathrm{t,CO}_2$ accurately reflects change in $P\mathrm{a,CO}_2$. Some studies have found a systematic increase in $P\mathrm{t,CO}_2$–$P\mathrm{a,CO}_2$ as $P\mathrm{a,CO}_2$ increases [34, 37] although others have found no such bias [35, 36]. There was no evidence of a systematic overestimation of $\Delta P\mathrm{a,CO}_2$ by $P\mathrm{t,CO}_2$ as $\Delta P\mathrm{a,CO}_2$ increased in these data (fig. 3). The authors therefore concluded that changes in $P\mathrm{t,CO}_2$–$P\mathrm{a,CO}_2$ across the night were due to sensor drift. After excluding from analysis subjects in whom drift was >1.33 kPa (10 mmHg), the authors corrected for drift using the morning $P\mathrm{a,CO}_2$ sample. The mean correction introduced was 0.21 ± 0.65 kPa (1.6 ± 4.9 mmHg).

Using these methods, SH, as measured by $P\mathrm{t,CO}_2$ was highly correlated with night-to-morning change in $P\mathrm{a,CO}_2$. Thus, while the authors cannot be certain of the precision of the $P\mathrm{t,CO}_2$ measurements, they believe they are likely to accurately represent trends in $P\mathrm{a,CO}_2$ across the night.

Definition of sleep hypoventilation. There is no universally accepted definition of SH. The recent consensus conference [4] chose a threshold value of an increase in $P\mathrm{a,CO}_2$ >1.33 kPa (10 mmHg) during sleep, without specifying a duration for this increase. The authors therefore chose a threshold increase of 1.33 kPa (10 mmHg) in $P\mathrm{t,CO}_2$. It was felt that 20% of TST constituted a significant portion of the night spent with

abnormally elevated P_{t,CO_2} levels. However, it is clear that the prevalence of SH will vary depending on the definition used. Figure 4 illustrates how prevalence changes depending on the increment in P_{t,CO_2}, which is defined as significant. Likewise, if SH is defined as >10% of TST spent at >1.33 kPa (10 mmHg) above baseline waking levels, the prevalence in this population would be 48%, if >40% of TST the prevalence would be 31%.

To conclude, the authors have found a high prevalence of sleep hypoventilation in a large hypercapnic chronic obstructive pulmonary disease population. Sleep hypoventilation was primarily related to baseline arterial carbon dioxide tension, body mass index and, in rapid-eye movement sleep to increased upper airway resistance. These patients often have increases in arterial carbon dioxide tension between night and morning, which are strongly related to the severity of sleep hypoventilation. Further studies are needed to investigate the long-term influence of repetitive increases in carbon dioxide due to sleep hypoventilation on respiratory drive and daytime blood gases in these patients.

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