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ORIGINAL RESEARCH

Sleep hypoventilation and daytime hypercapnia in stable chronic obstructive pulmonary disease

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Purpose: To explore the associations between sleep hypoventilation (SH) and daytime arterial pressures of carbon dioxide (P_aCO_2), sleep stages, and sleep apneas/hypopneas (AHI) in subjects with chronic obstructive pulmonary disease (COPD). SH has previously been found in COPD-subjects with chronic hypercapnic respiratory failure (CHRF) using supplementary oxygen (LTOT), and has been proposed as a possible predictor for CHRF.

Patients and methods: A prospectively designed observational study in a pulmonary rehabilitation hospital of 100 (39 male) stable COPD inpatients with a mean forced expiratory volume in 1 second (FEV_1) of 1.1 L (42% of predicted) and a mean age of 64 years, using polysomnography with transcutaneous measurement of carbon dioxide pressure increase ($\Delta P_{tc}CO_2$).

Results: SH as defined by the American Academy of Sleep Medicine (AASM) was found in 15 of the subjects, seven of whom used LTOT. However, six had SH despite being normocapnic during the daytime (only one on LTOT). Subjects with SH had a greater $\Delta P_{tc}CO_2$ increase from nonrapid eye movement (NREM) to rapid eye movement (REM) sleep stages compared to non-SH subjects (mean [standard deviation] between-groups difference =0.23(0.20) kPa, $P<0.0005$). Subjects with apnea/hypopnea index ≥15 (overlap, N=27) did not differ from those with COPD alone (AHI <5, N=25) in sleep $\Delta P_{tc}CO_2$ or daytime P_aCO_2. A regression model with the variables FEV_1, LTOT, and sleep maximum $\Delta P_{tc}CO_2$ explained 56% of the variance in daytime P_aCO_2 ($F(3, 94) = 40.37$, $P<0.001$).

Conclusion: In stable COPD, SH as defined by the AASM was found both in normocapnic, non-LTOT subjects and in hypercapnic, LTOT-using subjects. Between-sleep-stage increase in $\Delta P_{tc}CO_2$ was higher in subjects with SH. Overlap subjects did not differ from simple COPD subjects in sleep $\Delta P_{tc}CO_2$ or daytime P_aCO_2.

Keywords: blood gas analysis, etiology, physiopathology, carbon dioxide, polysomnography

Introduction

Chronic obstructive pulmonary disease (COPD) has a high and increasing morbidity and mortality worldwide, and is estimated to be the third leading cause of death by 2020.[1] Chronic hypercapnic respiratory failure (CHRF) is associated with poor prognosis in COPD. The pathophysiological mechanisms leading to CHRF are not fully established, but sleep is of particular interest as a state of unstable respiration. Blood gas sampling during sleep is difficult, as it can interfere with sleep architecture, and only a few studies of small populations have been published. In COPD, end-tidal measurement of carbon dioxide pressure is too inaccurate to substitute for arterial pressure of carbon dioxide (P_aCO_2);[3] however, transcutaneous measurement of carbon dioxide pressure ($P_{tc}CO_2$) minimally disturbs sleep, and $P_{tc}CO_2$ is now regarded by

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the American Academy of Sleep Medicine (AASM) as a surrogate for P_aCO_2.[4]

In normal sleep, changes in central respiratory control, muscle contractility, and lung mechanics lead to hypoventilation,[5–7] with arterial pressure of carbon dioxide increasing to as much as 0.9 kPa above supine, awake values.[8–10] In COPD this hypoventilation is more pronounced, especially during REM sleep, as a consequence of obstructed airflow, hyperinflation, respiratory muscle dysfunction, blunted ventilatory responses to hypercapnia and hypoxemia, ventilation/perfusion mismatch, and medications.[11] Poor sleep quality is often reported, and polysomnography has shown a reduced total sleep time, disturbances in sleep architecture, and highly frequent arousals.[12–15] Sleep hypoventilation was a common finding in two studies of stable, hypercapnic COPD subjects on long-term oxygen treatment (LTOT).[16,17] It is unclear whether this hypoventilation was mainly the result of supplementary oxygen. In COPD, daytime P_aCO_2 correlates inversely with the forced expiratory volume in 1 second (FEV_1),[18] and one study reported a more severe daytime hypercapnia in subjects with coexisting COPD and obstructive sleep apnea (overlap syndrome), compared to subjects with COPD or obstructive sleep apnea alone.[19] Sleep hypoventilation (SH) has recently been defined by the American Academy of Sleep Medicine as an increase of 1.3 kPa or more in P_aCO_2 during sleep, to a value exceeding 6.7 kPa for at least 10 minutes.[4]

Finding SH in normocapnic COPD subjects may be predictive of imminent hypercapnic respiratory failure, but to our knowledge, no studies have assessed SH in COPD subjects with normocapnia or in those with CHRF without LTOT.

The primary aim of this study was to determine whether SH is associated with daytime hypercapnia, with secondary aims to explore the impact of SH on the $P_{tc}CO_2$ increase between sleep stages, and whether SH or daytime P_aCO_2 is associated with the frequency of sleep apneas/hypopneas.

Material and methods

Subjects

Study participants were all Caucasians and inpatients at the Glittreklinikken Pulmonary Rehabilitation Hospital from January 2010 through June 2011. Initially, 60 subjects with P_aCO_2 <6.3 kPa and 60 with P_aCO_2 ≥6.3 kPa, all with Global initiative for Chronic Obstructive Lung Disease (GOLD)[20]-defined COPD, were to be included. Due to fewer hypercapnic subjects, these were oversampled by asking all to participate, whereas subjects with P_aCO_2 <6.3 kPa were selected randomly, stratifying for sex prior to participation request. In total, 166 subjects were screened for participation.

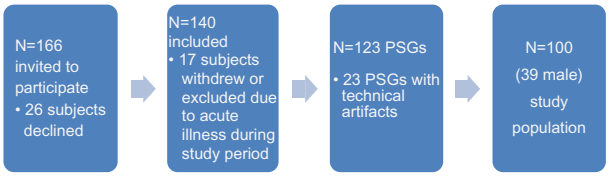

Figure 1 Study population.
Abbreviation: PSG, polysomnography.

The following exclusion criteria were used: diagnosed obstructive sleep apnea (OSA), COPD exacerbation within 3 weeks prior, other serious lung comorbidity (ie, cancer, sarcoidosis, restrictive lung disease) or diseases affecting thoracic or abdominal movement, unstable angina pectoris, hypertension, diabetes mellitus, myocardial infarction within last 3 months, cerebral infarction, and addiction to drugs, alcohol, or narcotics.

All subjects used prescribed medication, but no respiratory depressant drugs were taken from 48 hours prior to first polysomnography (PSG) recording until end of study. Sixty-six of the 166 subjects declined, withdrew, or were excluded. The main reasons for decline/exclusion included fear of being unable to sleep with electrodes on head and body and technical artifacts in $P_{tc}CO_2$-signal (Figure 1, further details in Supplementary material). The remaining 100 PSGs of spontaneous sleep were analyzed.

The protocol was approved by the Regional Ethics Committee in southeastern Norway.

Measurements

Arterial blood gas samples (PICO50, Radiometer, Copenhagen, Denmark) were collected after 10 minutes seated rest at approximately 2 pm prior to PSG recording, and analyzed within 10 minutes on a Radiometer ABL720Flex (Radiometer). At sampling, all subjects were breathing room air, with the exception of those on LTOT who used their prescribed dose of supplementary oxygen. Height, weight, and lung function tests including measurement of postbronchodilator spirometry, diffusing capacity of the lung (DLCO), and body plethysmography of total lung volumes (MasterScreen Pneumo, Jaeger-Toennies, Hoechberg, Germany) were recorded during first week at the hospital. Reference values were based on equations from the European Community for Coal and Steel.[21] PSG data was recorded with Embla A10 (Medcare Flaga, Reykjavik, Iceland) and $P_{tc}CO_2$ data with Tosca 500 (Radiometer, Basel, Switzerland) for two nights, the first night for acquaintance with the equipment, and

the second night recording sleep data online to a bedside computer with Somnologica Studio Version 3.3 software (Medcare Flaga). PSGs were only recorded on weekdays, with channel setup according to the 2007 recommendations from the AASM.[22] When the subject went to bed, a nurse started the recording with the subject watching TV or reading to stay awake while the signal from the Tosca probe stabilized. After approximately 30 minutes, the nurse turned off the light, this time being recorded as analysis started for the PSG. Rise time in the morning was recorded by the nurse. Subjects on LTOT used their prescribed dose of oxygen during PSG.

The $P_{tc}CO_2$ data were sampled with a frequency of 10 Hertz, with mean and maximum values calculated for each epoch of 30 seconds. Unpublished data collected at Glittreklinikken prior to the study showed equivalence between changes in $P_{tc}CO_2$ and P_aCO_2, but with a delay time of 54–57 seconds (see Supplementary material). Thus, $P_{tc}CO_2$ data were left-shifted two epochs. For each sleep stage in the PSG, the mean of each epoch's mean $P_{tc}CO_2$ values were calculated, while the epoch with the highest value was reported as the maximum $P_{tc}CO_2$.

Sleep scoring was done independently by two experienced polysomnographists. Ten PSGs were scored by another two polysomnographists to select the scorer with the best concordance (see Supplementary material). According to recommendations from the AASM,[22] a hypopnea was scored when nasal pressure dropped ≥30% for ≥10 seconds with ≥4% desaturation drop from baseline, with ≥90% of the event's duration meeting the amplitude reduction criteria for hypopnea (criterion A).

Statistical analysis

Data were assessed for normality of distribution and homogeneity of variance. Differences between groups were analyzed using Pearson chi-square test, Fisher's exact test, Mann–Whitney U test, and Student's *t*-test, differences within groups by Student's *t*-test. Relationships between groups were explored by chi-square tests for independence, within groups by Spearman's rho and multiple regressions. No violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity was found preliminary to regression analysis. Concordance was measured by Cohen's kappa. Two-sided *P*-values of ≤0.05 were considered significant, except in subgroup analyses of the SH subjects (N=15), in which two-sided $P \leq 0.01$ was applied. All analyses were performed using IBM SPSS Statistics version 19 (IBM Corporation, Armonk, NY, USA).

Results

As shown in Table 1, the group of 24 CHRF subjects had a greater increase in carbon dioxide pressure ($\Delta P_{tc}CO_2$) during sleep compared to the normocapnic subjects, and SH by the AASM definition (an increase of 1.3 kPa in the $P_{tc}CO_2$ during sleep compared with awake supine level to a value exceeding 6.7 kPa for at least 10 minutes) was more frequent.[4] Likewise, they had a higher median daytime base excess (BE), a lower P_aO_2, more frequent LTOT, and they were older and over-represented by females. However, no differences were found in total sleep time (TST), sleep stages as percent of TST, awakenings, arousals, apneas, or hypopneas (a table of sleep parameters according to age and compared to normal is provided in the Supplementary material). Oddly, no difference was found in body mass index (BMI); the mean BMI was 25 kg/m^2, and only 13 were obese (BMI ≥30 kg/m^2), whereas 26 were underweight (BMI <21 kg/m^2). As would be expected, the CHRF group had more severely obstructed airways with hyperinflation and impaired gas exchange, a shorter 6-minute walking distance (6MWD), higher dyspnea scores (modified medical research council questionnaire, COPD assessment test), and a higher BMI/obstruction/dyspnea/exercise capacity (BODE)-index.

The group of 15 SH subjects had a higher median daytime P_aCO_2, and LTOT was more frequent compared to the non-SH group (Table 1); likewise, median BE was higher. No differences were found between the SH and non-SH groups in other medication, sex, age, BMI, smoking habit, spirometry, or sleep parameters mentioned above.

On average, the 15 SH subjects were severely obstructed, with a median (interquartile range [IQR]) FEV_1 =0.80 (0.84) liters. Interestingly, however, six of the 15 SH-subjects were daytime normocapnic, with a median (IQR) P_aCO_2 of 5.00 (0.51) kPa, and only 1 used LTOT; this subgroup had a higher FEV_1 compared to the group of nine hypercapnic subjects (median [IQR] 1.45 (0.81) liters versus 0.63 (0.26) liters, *P*=0.002). However, BMI and sleep apneas/hypopneas (AHI) did not differ between the normocapnic and hypercapnic SH-subjects.

As illustrated in Figure 2, the median of mean $\Delta P_{tc}CO_2$ showed an increasing trend with deeper NREM sleep, and with the highest values in REM sleep, both in the non-SH group and in the SH group. A mean increase (standard deviation [SD]) from NREM to REM of 0.20 (0.16) kPa ($P<0.001$) was found in the non-SH group, whereas this increase was 0.46 (0.28) kPa ($P<0.001$) in the SH group, with the mean difference between the groups being 0.23 (0.20) kPa, ($P<0.0005$). The pattern of gradual increase

Table 1 Differences between subjects with and without CHRF and subjects with and without SH; values as median (interquartile range), N=100

	Normocapnic N=76[a]	CHRF N=24	*P*	No SH N=85	SH N=15	*P*
Demographic data						
Sex, female	41 (54)*	20 (83)*	0.010	49 (58)*	12 (80)*	0.102
Age, years	64 (11)	68 (15)	0.032	65 (11)	64 (15)	0.854
BMI, kg/m^2	25.5 (6.99)	22.9 (9.06)	0.199	24.8 (6.67)	27.1 (11.3)	0.916
Smoking habit						
Pack years	34 (23)	25 (18)	0.068	32 (22)	31 (26)	0.783
Current smoker	14 (18)*	2 (8)*	0.345	14 (17)*	2 (13)*	0.679
Spirometry						
FVC, % of pred[b]	79.5 (24.3)	57.0 (21.0)	0.000	73.5 (25)	67.0 (31.0)	0.841
FEV_1, % pred	43.0 (24.8)	25.0 (11.0)	0.000	40.0 (24.0)	34.0 (27.0)	0.296
FEV_1/FVC, ratio	0.46 (0.12)	0.37 (0.09)	0.000	0.44 (0.14)	0.40 (0.18)	0.185
DLCO, mmol/min/kPa[c]	3.59 (2.45)	2.44 (1.39)	0.000	3.34 (2.20)	2.89 (1.64)	0.385
RV/TLC, ratio[d]	0.57 (0.11)	0.72 (0.12)	0.000	0.60 (0.16)	0.65 (0.22)	0.297
Medication						
LTOT	3 (4)*	12 (50)*	0.000	8 (9)*	7 (47)*	0.001
SABA/LABA	71 (93)*	24 (100)*	0.333	80 (94)*	15 (100)*	1.00
Theophylline	3 (4)*	1 (4)*	1.00	4 (5)*	0 (0)*	1.00
Steroid po	2 (3)*	3 (13)*	0.088	5 (6)*	0 (0)*	1.00
Clinical data						
CAT, score	17.0 (6.0)	21.0 (6.0)	0.004	18.0 (7.0)	18.5 (7.0)	0.593
MMRC, score	2.0 (1.0)	3.0 (2.0)	0.000	2.0 (1.0)	2.0 (2.0)	0.561
6MWD, meter[e]	468 (173)	293 (110)	0.000	438 (186)	370 (203)	0.419
BODE index[f]	3.0 (3.0)	6.0 (2.0)	0.000	3.0 (3.0)	6.0 (5.0)	0.122
Laboratory data						
P_aO_2, kPa[g]	9.33 (1.47)	8.23 (1.84)	0.010	9.13 (1.64)	9.88 (2.28)	0.166
P_aCO_2, kPa	5.14 (0.76)	6.83 (0.68)	–	5.33 (0.945)	6.67 (2.09)	0.010
BE[h]	0.85 (1.91)	6.44 (3.79)	0.000	1.56 (2.86)	4.36 (5.94)	0.019
CHRF	–	–	–	15 (18)*	9 (60)*	0.001
Sleep time and awakenings						
TST, min	352 (76)	337 (112)	0.218	348 (77)	354 (92)	0.369
REM% TST	21.9 (7.2)	20.5 (10.7)	0.366	21.5 (7.8)	22.1 (10.4)	0.916
WASO, min	46 (43)	53 (109)	0.468	50 (70)	39 (32)	0.265
Awake	24 (16)	24 (25)	0.904	24 (17)	21 (19)	0.245
Sleep arousals						
TAI	16.7 (9.4)	20.2 (15.7)	0.116	17.3 (11.0)	14.4 (13.5)	0.466
AAI	1.3 (2.7)	1.6 (4.0)	0.862	1.30 (3.00)	1.80 (3.60)	0.888
HAI	2.8 (3.5)	2.0 (3.2)	0.183	2.60 (3.90)	2.60 (3.30)	0.714
Sleep apneas/hypopneas						
AHI	9.2 (10.5)	9.6 (13.5)	0.589	9.0 (10.4)	9.9 (14.0)	0.996
AHI ≥15	20 (26)*	7 (29)*	0.784	23 (27)*	4 (27)*	1.00

CAHI ≥ 1	3 (4)*	1 (4)*	1.00	4 (5)*	0 (0)*	1.00
MAHI ≥ 1	3 (4)*	2 (8)*	0.591	4 (5)*	1 (7)*	0.564
HI	5.3 (4.9)	4.6 (7.6)	0.274	5.2 (6.3)	5.3 (4.9)	0.798
Sleep hypoventilation						
Mean $\Delta P_{tc}CO_2$, kPa	0.44 (0.34)	0.54 (0.50)	0.081	0.40 (0.33)	0.88 (0.74)	**0.000**
Max $\Delta P_{tc}CO_2$, kPa	0.83 (0.41)	1.21 (0.81)	0.003	0.80 (0.37)	1.63 (0.91)	0.000
REM max $\Delta P_{tc}CO_2$, kPa	1.02 (0.51)	1.40 (1.16)	0.009	0.95 (0.51)	1.79 (0.67)	0.000
NR max $\Delta P_{tc}CO_2$, kPa	0.75 (0.40)	1.19 (0.78)	0.002	0.75 (0.35)	1.58 (0.91)	0.000
REM min S_pO_2, %	82.4 (11.2)	81.1 (25.7)	0.111	82.2 (10.7)	79.0 (31.7)	0.308
NR min S_pO_2, %	87.2 (6.7)	84.7 (19.3)	0.034	86.4 (7.0)	87.9 (10.7)	0.828
SH	6 (8)*	9 (38)*	0.001	–	–	–

Notes: Normocapnic, P_aCO_2 <6.3 kPa. *N (% of N) instead of median (interquartile range). [a]One missing P_aCO_2 replaced with value at arrival in the hospital =5.40 kPa. [b]N=99; one missing from routine spirometry, reason unknown. [c]N=84; 16 missing from DLCO because of insufficient vital capacity or because they could not hold their breath for 10 seconds. [d]N=91; nine missing from body pletysmography because of claustrophobia. [e]N=96; four missing from 6MWD, reason unknown. [f]N=93; seven missing from BODE index. [g]N=99; one missing from P_aO_2 and P_aCO_2; unable to hit artery. [h]N=98; two missing from S_pO_2 and BE, technical problem with analysis.

Abbreviations: 6MWD, 6 minutes walking distance; AAI, apnea arousal index; AHI, apnea/hypopnea index; Awake, number of awakenings after sleep onset; BE, base excess in arterial blood; BMI, body mass index; BODE, BMI/obstruction/dyspnea/exercise capacity; CAHI, central AHI; CAT, COPD assessment test; CHRF, chronic hypercapnic respiratory failure ($P_aCO_2 \geq 6.3$ kPa); DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume first second; FEV_1 % of pred, FEV_1 percentage of predicted; FVC, forced vital capacity; FVC % of pred, FVC percentage of predicted; HAI, hypopnea arousal index; HI, hypopnea index; LTOT, long-term oxygen therapy; MAHI, mixed AHI; Max $\Delta P_{tc}CO_2$, maximum sleep increase in transcutaneous carbon dioxide from awake, supine rest; Mean $\Delta P_{tc}CO_2$, mean sleep increase in transcutaneous carbon dioxide from awake, supine rest; MMRC, modified medical research council questionnaire; NR max $\Delta P_{tc}CO_2$, as above in non-REM sleep; NR min S_pO_2 non-REM sleep minimum oxygen saturation measured by pulse oximetry; P_aCO_2, arterial pressure of carbon dioxide; P_aO_2, arterial pressure of oxygen; REM% TST, rapid eye movement – sleep percentage of total sleep time; REM max $\Delta P_{tc}CO_2$, as above in REM sleep; REM min S_pO_2, REM sleep minimum oxygen saturation measured by pulse oximetry; RV, residual volume; SABA/LABA, short/long acting beta-two receptor agonist; SH, sleep hypoventilation according to American Academy of Sleep Medicine definition; steroid po, oral prednisolone; TAI, total arousal index; TLC, total lung capacity; TST, total sleep time; WASO, minutes awake after sleep onset.

with deeper sleep was not found for the median of maximum $\Delta P_{tc}CO_2$ (Figure 2), especially as the values in N3 sleep were lower compared to N2. In subjects without SH the N2–N3 mean $\Delta P_{tc}CO_2$ decrease (SD) was –0.13 (0.16) kPa ($P<0.001$), whereas the SH group had a mean decrease of –0.36 (0.41) kPa ($P=0.005$); the mean difference between the groups was 0.35 (0.31) kPa ($P=0.002$).

With an AHI cutoff at 15/hour, concordance between the two controllers and the chosen polysomnographist was good (Kappa =1.00 between all three scorers, N=10, $P=0.002$). Despite exclusion of subjects with diagnosed OSA prior to study, only 25 subjects had AHI <5/hour, whereas 27 had AHI ≥15/hour; the latter chosen to define overlap syndrome as no record of daytime sleepiness was available, while COPD alone was defined by AHI <5/hour. Central and mixed apneas were found in 28 and 27 subjects, respectively, 4 having central apnea/hypopnea index ≥1/hour (highest value 4.4/hour), and five having mixed apnea/hypopnea index ≥1/hour (highest value 14.1/hour). Subjects with central and mixed apneas were included for overlap analysis (Table 2). As expected, the 27 overlap subjects had a significantly lower minimum S_pO_2 compared to the 25 COPD subjects, both in REM and in NREM sleep. Notably, however, the overlap subjects did not differ from those with COPD in sleep $\Delta P_{tc}CO_2$ or daytime P_aCO_2 (Table 2), nor in the frequency of SH (15% in COPD versus 16% in the overlap group, $P=1.00$).

Finally, as sleep hypoventilation by various definitions previously has been found in severe COPD with CHRF and LTOT,[16,17] a hierarchical multiple regression was performed to assess whether the maximum CO_2 increase during sleep (sleep max $\Delta P_{tc}CO_2$) independently predicts daytime P_aCO_2 when controlling for COPD severity (FEV_1) and the use of LTOT. FEV_1 (liters) and LTOT (yes/no) were entered at Step 1, explaining 52% of the variance in daytime P_aCO_2. After entry of sleep max $\Delta P_{tc}CO_2$ (kPa) at Step 2, the total variance explained by the model was 56%, $F(3, 94) = 40.37$, $P<0.001$. Thus, sleep max $\Delta P_{tc}CO_2$ explained an additional 4% of the variance in daytime P_aCO_2 after controlling for LTOT and FEV_1, R square change =0.043, F change (1, 94) =9.24, $P=0.003$. In the full model, FEV_1 recorded the highest beta value (–0.44, $P<0.001$) over LTOT (0.39, $P<0.001$) and sleep max $\Delta P_{tc}CO_2$ (0.22, $P=0.003$).

Discussion

As previously shown by others, we find SH to be common in stable COPD subjects with CHRF using LTOT. However, the novelty in this study is that SH is also found in COPD

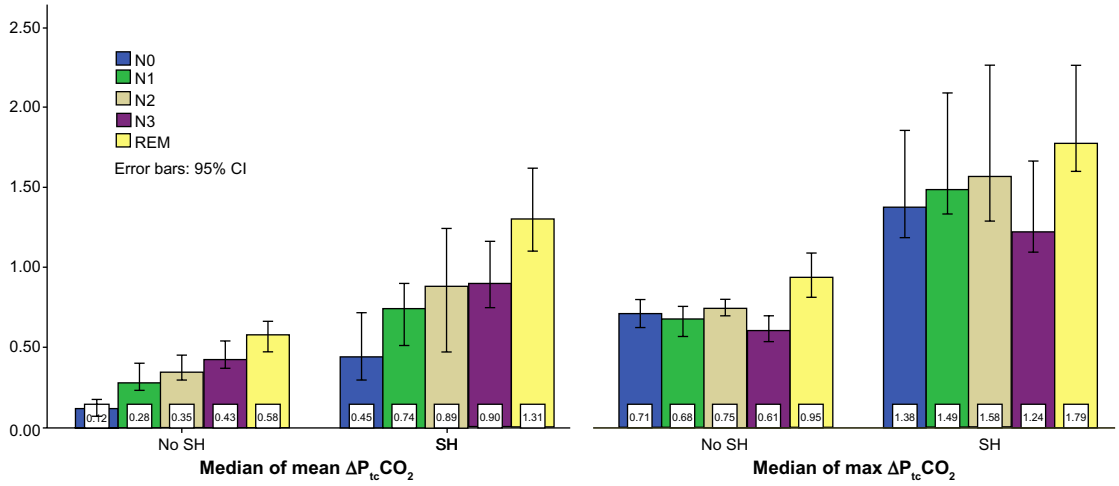

Figure 2 $\Delta P_{tc}CO_2$ according to sleep stages.
Notes: Each bar represents the sleep stage median value of the mean, and alternatively the maximum $\Delta P_{tc}CO_2$ in kPa. The first and third cluster represent the group with no SH; the second and fourth cluster represent the group with SH.
Abbreviations: $\Delta P_{tc}CO_2$, increase in carbon dioxide from supine, awake rest before sleep; N0, stage N0 sleep; N1, stage N1 sleep; N2, stage N2 sleep; N3, stage N3 sleep; REM, rapid eye movement sleep; SH, sleep hypoventilation according to American Academy of Sleep Medicine definition.

with CHRF without LTOT, and even in some normocapnic, non-LTOT subjects. We also find the mean $P_{tc}CO_2$ increasing with depth of sleep, the between-sleep-stage differences being greater in subjects with SH. Finally, overlap subjects in this study do not differ from COPD subjects in SH or in daytime P_aCO_2.

O'Donoghue et al found SH in 43% of 54 stable COPD subjects with CHRF, all using LTOT, when defining CHRF as daytime P_aCO_2 >6.12 kPa and SH as a $\Delta P_{tc}CO_2$ increase of ≥1.33 kPa for ≥20% of total sleep time.[17] Likewise, Tarrega et al studied stable, hypercapnic COPD subjects on LTOT and found nocturnal hypoventilation (NHV) in 21% of their 80 subjects, defining NHV as an increase in P_aCO_2 >1.33 kPa in any nocturnal blood gas sample as compared to the awake levels.[16] Using the AASM definition, we find SH in 15% of our 100 subjects, and in seven of the 15 (47%) subjects on LTOT. Hence, this study supports O'Donoghue et al and Tarrega et al in the notion of SH being commonly found in COPD with CHRF using LTOT. Finding SH in three subjects with CHRF not using LTOT indicates that SH is associated with daytime P_aCO_2 independent of LTOT. However, CHRF is not necessary either, as SH was also found in five normocapnic, non-LTOT subjects.

Table 2 Blood gases in COPD and overlap subjects, as median (interquartile range), N=52

	COPD AHI <5 N=25	Overlap AHI ≥15 N=27	*P*-value
Sleep			
Mean $\Delta P_{tc}CO_2$, kPa	0.34 (0.43)	0.54 (0.29)	0.117
Max $\Delta P_{tc}CO_2$, kPa	0.76 (0.56)	0.94 (0.50)	0.101
REM max $\Delta P_{tc}CO_2$, kPa	0.86 (0.51)	1.18 (0.69)	0.210
NREM max $\Delta P_{tc}CO_2$, kPa	0.71 (0.59)	0.89 (0.49)	0.117
REM min S_pO_2, %	87.0 (7.7)	78.0 (10.0)	0.000
NREM min S_pO_2, %	88.5 (5.6)	83.0 (11.2)	0.001
Awake			
P_aO_2, kPa[a]	9.51 (1.92)	9.11 (1.92)	0.059
P_aCO_2, kPa[a]	5.36 (2.12)	5.38 (1.43)	0.880
S_aO_2, %[b]	96.2 (3.2)	95.3 (3.4)	0.251

Notes: Prevalence of overlap could not be calculated as data on daytime sleepiness was not available. [a]N=24 in COPD group; one missing from P_aO_2 and P_aCO_2, unable to hit artery. [b]N=23 in COPD group; two missing from S_pO_2 due to technical problem with analysis.
Abbreviations: AHI, apnea/hypopnea Index; Max $\Delta P_{tc}CO_2$, maximum increase in transcutaneous carbon dioxide pressure from supine, awake rest; Mean $\Delta P_{tc}CO_2$, mean increase in transcutaneous carbon dioxide pressure from supine, awake rest; min S_pO_2, minimum oxygen saturation measured by pulse oximetry; NREM, nonrapid eye movement sleep; REM, rapid eye movement sleep; P_aCO_2, arterial pressure of carbon dioxide; P_aO_2, arterial pressure of oxygen at 2:00 pm prior to sleep; S_aO_2, arterial oxygen saturation; COPD, chronic obstructive pulmonary disease.

Figure 2 illustrates the mean $P_{tc}CO_2$ increase with sleep stages, and the greater between-stages increase in subjects with SH versus without SH, supporting the notion that SH in COPD primarily is the consequence of a failing respiratory pump. As arterial CO_2 increases due to hypoventilation, the brains' extracellular fluid bicarbonate builds up, blunting the central ventilatory drive, which in turn will lead to further elevation of CO_2.[23] In patients without COPD this vicious circle is broken by an arousal when P_aCO_2 reaches 7.3–8.7 kPa.[24] As changes in $P_{tc}CO_2$ are too sluggish in comparison to P_aCO_2, and in lack of a control group, this study did not provide data comparable to an arousal threshold. However, considering normal sleep maximum ΔPCO_2 is in the range of 0.3–0.9 kPa,[8] our findings of maximum $\Delta P_{tc}CO_2$ values of 1.2–1.8 kPa (Figure 2) suggests that COPD subjects with

SH have elevated CO_2 thresholds. With the increased levels of $\Delta P_{tc}CO_2$ and BE in subjects with SH, an elevated arousal threshold would be expected, hence unchanged frequencies of arousals and awakenings. Indeed, we find no significant differences in arousals, number of awakenings, or minutes of REM sleep percentage of TST between subjects with or without SH (Table 1). The lowest NREM $\Delta P_{tc}CO_2$ values recorded in stage N3 both in SH and non-SH subjects (Figure 2) is in line with the normal hypercapnic ventilatory response described by Douglas et al.[25]

The overlap subjects do not differ from those with COPD alone in the frequency of SH, in sleep CO_2-increase or in daytime P_aCO_2 (Table 2), neither are there significant differences in AHI between subjects with SH versus without SH (Table 1). This can be explained by the heterogeneity of COPD, as both the lungs (gas exchange system) and the respiratory pump (ventilatory system) are affected in various degrees of severity. Frequent apneas/hypopneas are not likely to result in sleep hypercapnia in patients with well-functioning respiratory pumps, as the retained CO_2 following an apnea/hypopnea will be exhaled during the next few breaths. When scoring PSG in severely hyperinflated COPD patients, however, desaturation events resulting from a failing diaphragm can be classified as hypopneas or apneas, thus contributing to the AHI, even though there is no obstruction of the upper airways (as in OSA). In this case, one would expect to find AHI correlated to sleep CO_2 increase. Hence, severe COPD with frequent apneas/hypopneas will be classified as overlap syndrome regardless of the etiology of the desaturation events.

Contrary to the findings of Resta et al,[19] we did not find a significant difference in daytime P_aCO_2 in the overlap group as compared to the COPD group (Table 2). A main anthropometric difference between the study populations is body weight, as Resta et al reported a mean BMI of 36 kg/m^2 in the overlap versus 31 kg/m^2 in the COPD group, while our subjects had a median BMI of 25 kg/m^2 with no significant differences between overlap and COPD subjects. In a multiple regression model, Resta et al found the best predictors of P_aCO_2 in overlap subjects to be P_aO_2, FEV_1, and weight, O'Donoghue et al found the severity of SH in COPD subjects best predicted by a combination of baseline P_aCO_2, BMI, and percent REM sleep,[17] and Tarrega et al found NHV related to BMI.[16] Obesity might therefore explain the discrepancy between the findings of Resta et al and our findings.[19]

The variables FEV_1, use of LTOT, and sleep maximum $\Delta P_{tc}CO_2$ explain 56% of the variance in daytime P_aCO_2. A low FEV_1 can indicate poor function of the respiratory pump (chronic obstruction leading to hyperinflation); LTOT is known to affect the central respiratory drive to breathe,[26] and increased sleep $\Delta P_{tc}CO_2$ can indicate a blunted respiratory drive as a consequence of the failing respiratory pump. However, the intriguing subgroup of five normocapnic, non-LTOT SH subjects does not fit in the picture, as they were not obese, nor severely obstructive or hyperinflated, and they had a median AHI of only 12.8/hour. Thus, their respiratory pump should have sufficient reserves to expel CO_2 even during REM sleep.

To our knowledge, there are no previously published studies with PSG and $P_{tc}CO_2$ data from COPD subjects including as many as 100 subjects. This study has its limitations, however. First, as previous studies indicate the prevalence of OSA being the same in COPD as in the normal population,[27] the study protocol did not include collection of daytime sleepiness data. Hence, the diagnosis of overlap syndrome based exclusively on the AHI is admittedly uncertain, and prevalence could not be analyzed. However, as OSA is defined either by AHI $\geq$5 and daytime sleepiness symptoms or AHI $\geq$15 in asymptomatic subjects,[28] we chose the latter to define overlap; the most conservative criterion would include only certain OSA subjects in this group, whereas AHI $<$5 was chosen to define subjects with COPD alone, thus reducing the risk of masking any differences between overlap and COPD groups.

Second, we do not regard the demographic profile in this study as representative for the entire COPD population in Norway, as a selection bias can be present for several reasons, including the referral/selection for lung rehabilitation, the oversampling of subjects with P_aCO_2 $\geq$6.3 kPa, and subjects declining to participate. As the study population had a somewhat high BODE index of 4, indicating a 4-year mortality of about 32%,[29] the results presented does not reflect the status of the entire COPD population, and the prevalence of SH is undoubtedly lower in patients with mild COPD.

Third, as arterial blood gas samples from the subjects using LTOT were collected when using their prescribed oxygen flow, the PO_2 and PCO_2 referred in Table 1 do not reflect the untreated values of the study population. However, as all subjects on LTOT were stable and adapted to their supplementary oxygen, blood gases measured reflects their habitual status.

Conclusion

Sleep hypoventilation as defined by the AASM is frequently found in subjects with severe COPD and CHRF using supplementary oxygen. The novelty of this study is the finding of SH

also in CHRF without LTOT, and even in some normocapnic, non-LTOT subjects with only moderate COPD. The carbon dioxide pressure increases with deeper sleep, with differences between sleep stages being greater in subjects with SH than those without SH. Subjects with AHI ≥15/hour (overlap) do not differ from those with AHI <5 (COPD alone) in SH, sleep $\Delta P_{tc}CO_2$, or in daytime P_aCO_2. A regression model with the predictors FEV_1, LTOT, and sleep maximum $\Delta P_{tc}CO_2$ explains half of the variance in daytime P_aCO_2.

SH is currently used in clinical practice at some centers as an independent indicator for the initiation of noninvasive positive pressure ventilation in COPD,[30] and correction of nocturnal $P_{tc}CO_2$ to normocapnic values has shown to improve lung function and may improve survival.[31,32] To the best of our knowledge, however, no case-control or prospective studies have been undertaken to investigate the exact mechanisms behind SH or SH's role as a predictor for CHRF, so further research is clearly needed.

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Disclosure

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Supplementary material

Subjects

Reasons given from the 26 subjects not participating: Anxiety/fear of not being able to sleep with electrodes connected to head/body (ten subjects); not willing to discontinue sedentary medication (three subjects); fear that sleep studies would interfere with the rehabilitation program (three subjects); did not want sleep investigated (three subjects); fear of pain from blood gas sampling (two subjects). Two subjects declined because an interventional part of the project (not published) implied sleeping with supplementary oxygen or taking alcohol or zopiclone before sleep for a third polysomnography. One subject did not want to be seen with wires connected to the head, one needed to go outdoors for smoking at night and one did not give a reason.

Reasons for drop out of 17 subjects after initial consent given: Felt it impossible to sleep with wires on the body (seven subjects); exacerbation of COPD (six subjects); technical or protocol failure (two subjects); illness/disease of other cause (one subject); medication which excluded (one subject).

Twenty-three polysomnographies were excluded because of technical artifacts in transcutaneous measurement of PCO_2; 17 because the $P_{tc}CO_2$ probe periodically lost contact with skin (low $P_{tc}CO_2$-signal); six because the probe was compressed by pillow or hand/arm (high $P_{tc}CO_2$-signal).

$P_{tc}CO_2$ versus P_aCO_2

The correlation between P_aCO_2 and $P_{tc}CO_2$ has been studied in stable subjects with lung diseases,[1] in critically ill subjects,[2–5] during cardio-pulmonary exercise testing[6] and in circulatory stable subjects; both inactive and during exercise.[7,8] Conclusions varied as to whether $P_{tc}CO_2$ can substitute P_aCO_2. Hence, clinical data were obtained from 18 stable, supine COPD subjects with an indwelling catheter at Glittreklinikken (mean FEV_1(SD)=46(26)% of predicted, N=4 had $P_aCO_2 > 6.3$ kPa). Every twentieth minute for up to six hours a pair of P_aCO_2 and $P_{tc}CO_2$ values were recorded. From 204 pairs, a mean difference (SD) $P_{tc}CO_2 - P_aCO_2$ of 0.233 (0.312) kPa was found; this SD regarded as too high a variance to let the absolute values of $P_{tc}CO_2$ substitute those of P_aCO_2. However, the within subject mean difference (SD) $P_{tc}CO_2 - P_aCO_2$ was 0.229 (0.186) kPa. We concluded that the within subject SD of <0.2 kPa indicates that the changes in $P_{tc}CO_2$ can substitute the changes in P_aCO_2. Consequently, when studying COPD subjects with PSG and $P_{tc}CO_2$ we recorded the changes in $P_{tc}CO_2$ during sleep, not the absolute values.

$P_{tc}CO_2$ delay time

To find the time delay from an alveolar change in PCO_2 until the first response in $P_{tc}CO_2$, we studied nine COPD subjects (six male) with a mean FEV_1(SD) of 41(20)% of predicted, and $P_aCO_2 < 6.3$ kPa. The supine subjects wore a tight fitting face mask, inlet selecting either room air or a gas mixture of 4% CO_2 in air. Data were collected in three phases, each lasting 200 sec: 1) stable phase breathing room air; 2) increasing phase breathing 4% CO_2; and 3) decreasing phase after switching back to room air. $P_{tc}CO_2$ was recorded every 5th second for 2 minutes, then every 10th second in each phase. Arterial blood samples were taken from an

Table S1 Sleep parameters according to age, compared to reference populations with normal lung function, N=100

Age groups	46–59 years Results (Reference values*) N=29		60–69 years Results (Reference values*) N=47		70–82 years Results (Reference values^) N=24	
	Mean	SD	Mean	SD	Mean	SD
Sleep summary						
TST, min	347 (367)	56.7 (58.0)	360 (349)	54.0 (51.5)	296 (335)	56.3 (na)
Awake	21 (9.7)	9.1 (5.2)	27 (14.6)	12 (6.7)	36 (na)	30.1 (na)
WASO, min	40 (na)	40 (na)	60 (na)	39 (na)	105 (75)	61 (na)
SES,%	90 (90)	11 (7.1)	86 (9.1)	86 (7.9)	74 (82)	15 (na
Sleep stage percentage of total sleep time						
N1	13 (5.2)	6.6 (4.2)	17 (4.8)	7.1 (3.3)	21 (12)	11.7 (na)
N2	39 (63)	8.4 (17)	41 (68)	7.3 (13)	37 (56)	10 (na)
N3	26 (8.8)	9.4 (7.3)	21 (8.7)	11 (7.9)	22 (13)	12 (na)
REM	22 (23)	7.2 (7.5)	21 (19)	6.2 (8.5)	20 (19)	8.5 (na)

Notes: *Reference values according to M. Hirschkowitz et al[9]

^Reference values according to M. Ohayon et al (adapted from graph)[10]

Abbreviations: TST, total sleep time; Awake, number of awakenings; WASO, minutes wake after sleep onset; SES, sleep efficiency from sleep start; N1, stage N1 sleep; N2, stage N2 sleep; N3, stage N3 sleep; REM, rapid eye movement sleep; na, not available.

indwelling catheter three times during phase 1), every 5th second the first 30 sec of phase 2) and 3), then every 30th second for a total of 150 seconds. The results showed a first response time (frt) meaning time from change in alveolar PCO_2 to $P_{tc}CO_2$>2SD off stable phase as follows: Mean frt(SD) in increasing phase: 54(5,6) sec; Mean frt(SD) in decreasing phase: 57(15) sec. For arterial PCO_2: 13,3(5,6) sec and 11,7(2,5) sec, accordingly.

Sleep scoring

All PSG's were initially scored by two independent, registered polysomnographists (RPSG's) blinded to subject data except sex, age, height and weight. As the scorings from these two RPSG's differed substantially on several sleep parameters (eg, AHI, HI, sleep stages) a random selection of 10 PSG's were scored by another two RPSG's who were blinded regarding the results from the first two scorers. The scorings from the initial RPSG with the best match to the last two RPSG's were then selected for data analysis.

Results, table supplement

When compared to normal subjects,[9,10] the study-subjects had twice to threefold more awakenings and N1-sleep. However, they had a normal amount of REM-sleep and about twice the percentage of slow wave (N3) sleep (table 1).

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