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Original research article

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Please cite this article as: Hansson D, Andersson A, Vanfleteren LEGW, *et al*. Clinical impact of routine sleep-assessment by peripheral arterial tonometry in patients with Chronic Obstructive Pulmonary Disease. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00458-2022).

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Clinical impact of routine sleep-assessment by peripheral arterial tonometry in patients with Chronic Obstructive Pulmonary Disease

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Word count

Abstract	250
Main text	3360
Number of figures	3
Number of tables	4
References	46

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Abstract

Background: Coexisting obstructive sleep apnoea (OSA) in patients with chronic obstructive pulmonary disease (COPD), defined as overlap syndrome (OVS), is prevalent and underdiagnosed. Routine assessment of OSA is not common practice in COPD care. Our study assessed the clinical impact of sleep-assessment by peripheral arterial tonometry (PAT) in COPD patients.

Methods: 105 COPD patients (mean age 68.1±9 years, BMI 28.3±6.0 kg/m^2, 44% males, GOLD stages I to IV in 2%, 40%, 42%, and 16%, respectively) underwent assessment at an outpatient COPD-clinic including anthropometrics, arterial blood gas (ABG) and spirometry in this clinical cohort study, PAT-based sleep studies were performed. Predictors of OVS and ABG were determined. Rapid Eye Movement (REM) sleep-related OSA was analyzed in OVS.

Results: 49 COPD patients (46%) suffered from moderate to severe OSA (OVS group, mean AHI 30.8±18 n/h, REM-Oxygen Desaturation Index (REM-ODI) 26.9±17 n/h). OVS was more prevalent in males compared to females (59% and 37%, P=0.029, respectively). Age (70.1±8 versus 66.3±10 years), BMI (30.0±6 versus 26.4±7 kg/m^2) and hypertension prevalence (71% versus 45%) were elevated (all p<0.03, respectively), while deep sleep (12.7±7% and 15.4±6%, p=0.029) and mean overnight oxygenation (90.6±3% and 92.3±2%, p=0.003) were lower in OVS compared to COPD alone. REM-ODI was independently associated with daytime pCO_2 (β=0.022, p<0.001). REM-OSA was associated with an elevated prevalence of atrial fibrillation (25% and 3%, P=0.022).

Conclusions: OVS was highly prevalent, specifically in obese males. REM-related OSA showed strong association with elevated daytime pCO2 and prevalent cardiovascular disease. PAT was feasible for sleep assessment in COPD.

Keywords: Obstructive sleep apnoea, REM-related OSA, intermittent hypoxia, epidemiology, diagnosis, arterial blood gases

Introduction

The combination of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA), often described as overlap syndrome (OVS), is common as both COPD and OSA are highly prevalent diseases.(1-4) Pathophysiological mechanisms include the reduction of supine residual function capacity, dynamic hyperinflation, reduction in nocturnal respiratory drive, and increased respiratory instability, all leading to sleep-hypoxemia.(5) Both COPD and OSA have been associated with adverse health outcomes, including cardiometabolic disease and malignancy. (6-9) Cardiovascular morbidity and mortality in OVS are higher than morbidity and mortality associated with COPD and OSA alone. (10, 11) Cohort studies suggest that the added risk related to OVS may be reduced by Positive Airway Pressure (PAP) treatment of OSA.(11-13) Therefore, management of OSA in COPD is recommended by the current GOLD guidelines. (14)

OVS is still commonly undiagnosed as clinical features and questionnaires lack sensitivity and often overlap with symptoms of COPD alone. (15) Limited access to simple sleep diagnostic procedures in COPD patients is currently a major obstacle as polysomnography, the gold-standard method, is not widely available and is cumbersome for the patient. Indeed, the use of thoraco-abdominal belts or naso-oral cannula and thermistors may introduce added discomfort during the already disturbed sleep in patients with COPD. Simplified sleep diagnostic methods like cardiorespiratory polygraphy or oximetry alone may increase availability and feasibility, but those techniques do not provide information on actual sleep time and sleep stage related respiratory events. This is a significant shortcoming, as recent knowledge suggests that respiratory events during Rapid Eye Movement (REM)-sleep are more strongly associated with negative health-outcomes when compared to respiratory events indices obtained during the entire night. (16-18) Hence, optimal sleep assessment strategies to confirm OVS remains to be established.

Peripheral arterial tonometry (PAT) is a portable diagnostic technique that has been validated for the diagnosis of OSA. (19, 20) The technology is less intrusive and studies in patients with suspected OSA showed reasonable diagnostic accuracy when compared with polysomnography (21), those studies were confirmed also among COPD patients. (22, 23) With the ambition to unwind some of the current knowledge-gaps, we studied sleep in a cohort of patients referred to a COPD outpatient clinic. Our aims included the assessment of

A) the prevalence of OVS in this COPD-cohort, B) the prevalence and impact of REM-related sleep apnoea in OVS, C) the associations between sleep related respiratory measures and daytime arterial blood gases, and D) the feasibility of the PAT sleep-diagnostic technology.

Methods

We conducted a cohort study at the COPD outpatient clinic at Sahlgrenska University Hospital, Gothenburg, Sweden, between April 2018 and May 2019. As part of the integration of sleep medicine in the routine assessment of COPD patients, new referrals to the COPD center from primary and tertiary care were recruited for the study. Inclusion criterion was a confirmed COPD diagnosis and the willingness to participate in the sleep evaluation. Sleep complaints and daytime sleepiness were assessed in the medical history by physicians experienced in sleep medicine. Exclusion criteria were a previously known diagnosis of OSA, already established home ventilation therapy, and not being able to communicate in Swedish or English. The study was approved by the regional ethical review board (Dnr 178-18, amendment Dnr 2019-02929). Informed and signed consent was obtained from all participants.

Post-bronchodilator spirometry was performed to assess forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the FEV_1/FVC ratio. The classification of airflow limitation severity (FEV_1% of predicted - Stage I: FEV_1>80%, II FEV_1 50-80%, stage III: FEV_1 30-50%; stage IV: FEV_1 <30%) was based on GOLD and the reference population of Hedenström. (14, 24) Daytime arterial blood gases (ABG), anthropometric data, and comorbidities were collected in all patients as part of the clinical routine. Clinical symptoms of COPD and sleep apnoea were evaluated by means of standardized questionnaires including the Medical Research Councils dyspnoea scale (mMRC), the COPD Assessment Test (CAT) and the Epworth Sleepiness Scale (ESS).

Overnight sleep was recorded at home using PAT (WatchPAT 200, Itamar Medical, Israel) and recordings were analyzed with the zzzPAT software (Itamar Medical, Israel). WatchPAT 200 is a device worn around the wrist with a PAT probe attached to one finger. A built–in actigraphy and a sensor attached on the apex of the sternum to record chest movements and snoring is included. Automated analysis of PAT amplitude, PAT derived pulse rate variability and actigraphy were used for the classification of sleep into the four stages: wakefulness, light sleep, deep sleep and REM sleep. (19) Sleep-disordered breathing was identified using the

information gained from the PAT signal, oxygen desaturation recorded with the PAT probe, pulse rate changes, snoring and chest movements. (25) Central versus obstructive respiratory events were classified using the sensor based on the sternum (data not reported due to very few central events). (26) Derived parameters for further analysis included sleep time, sleep efficiency, apnoea-hypopnoea index (AHI) and 4% oxygen desaturation index (ODI) separated for the entire sleep period, REM- and non-REM sleep. We defined sleep apnoea severity according to established cut-offs from mild, moderate to severe OSA with AHI 5 - ≤ 15 n/h, 15 - ≤ 30 n/h, and ≥30 n/h, respectively. OVS was defined as the combination of verified COPD diagnosis (spirometry and symptoms) and clinically relevant AHI ≥15n/h (27) . We further defined REM-related OSA in OVS patients according to strict criteria (28) as AHI all night ≥15n/h (as part of the OVS definition), REM-AHI to NREM-AHI ratio at least 2, REM sleep duration at least 30 minutes, REM-AHI at least 15 n/h.

Statistics

Descriptive analysis of the patient cohort was performed by calculating means and standard deviation (SD, normally distributed data) or median and interquartile range (IQR, not normally distributed data) for continuous data and percentages for categorical data. Between group differences were analyzed with student t-test and non-parametric test for normally or not normally distributed data, respectively. Chi^2 test was used for comparison of categorical variables. Predictors of an OVS diagnosis were determined by logistic regression analysis adjusting for age, BMI and gender. Generalized Linear Model (GLM) analysis adjusting for age, gender, body mass index (BMI), FEV_1 and sleep apnoea indices (AHI, ODI, REM-ODI) was applied to predict day-time arterial blood gases (pO_2, pCO_2). ABG analysis was performed in 97 patients (50 COPD alone, 47 OVS) with missing data in the remaining patients. Statistical analyses were performed using SPSS (version 26, IBM, United States). $P<0.05$ was considered as significant.

Results

Participants

One hundred and five COPD patients were included in the study. The cohort is characterized by female dominance (56.2%), a mean age of 68.1±9 years, and a mean BMI of 28.3±6 kg/m^2. (**Table 1**) Eighty-seven (83%) patients were classified as COPD severity class II or III according to lung function. The PAT sleep test was successfully performed in 104 patients. One patient was incapable to perform the test at home and was assessed by in-lab cardiorespiratory polygraphy (sleep stage data not available).

Prevalence of sleep apnoea

COPD without OSA was found in 21% of patients whereas the prevalence for mild OSA was 33%. Moderate to severe OSA, which defined the patients with OVS, accounted for 46% of patients. OVS was more prevalent in males compared to females (59% and 37%, p=0.029, respectively) (**figure 1**). OSA prevalence and severity were not associated with COPD stages I-IV, the OVS prevalence was 50%, 45%, 52%, and 31% in COPD classes I-IV, respectively, p=0,55.

Clinical characteristics

Patients with OVS were older, more obese, and more frequently of male gender when compared with patients suffering from COPD alone (**Table 1**). Spirometry data were not different between the two groups. In contrast, the prevalence of cardiovascular disease like systemic hypertension, ischemic heart disease, and chronic heart failure were all significantly more prevalent in OVS patients whereas a history of stroke was more prevalent in COPD alone. Daytime ABG analysis revealed significantly lower pO_2 and higher pCO_2 in patients with OVS compared with COPD alone (**Table 1**).

COPD symptom-burden assessed by mMRC dyspnoea and CAT was comparable between the two groups (**Table 1**). Furthermore, OVS patients did not differ regarding the degree of daytime sleepiness from patients with COPD alone. In a multivariate regression analysis, including age, gender, lung function (FVC, FEV_1), BMI, and the patient reported symptoms reported earlier, BMI (t =2.25, ß=0.270, p=0.014) was the single independent predictor of OVS.

Sleep analysis

For the entire study cohort, mean total sleep time was 6.2±1.7h with a sleep efficiency of 80.2±11%. The proportion of deep sleep was 14.1±6.4% and REM sleep accounted for 20.0±7% of the total sleep time (**Table 2**). Among OVS patients compared with COPD alone, we identified decreased deep sleep (12.7 ± 6.7 versus 15.4 ± 5.9%, p=0.029). By definition, all indices reflecting sleep apnoea intensity and apnoea-related intermittent hypoxia were significantly more pronounced in the OVS- compared with the COPD alone group. (**Table 2**). Mean overnight oxygen saturation was significantly lower in patients with OVS (90.6±3 and 92.3±2, p=0.003).

REM-related OSA in OVS patients

REM sleep was short in four OVS patients and REM-AHI index was not calculated. REM-related OSA was observed in 12 out of 45 OVS patients (27%). Anthropometric data, lung function, ABG, and symptoms did not differ between REM- and Non-REM related OSA. Sleep duration, all night AHI, and Non-REM AHI were all significantly lower in REM-related OSA (**Table 3**). However, the prevalence of systemic hypertension (92% versus 64%, P=0.069) and atrial fibrillation (25% and 3%, P=0.022) were higher in the OVS subgroup with REM-related OSA. (**Figure 2**)

Arterial blood gas analysis

Regression analyses using GLM identified independent predictors for daytime arterial blood gases. (**Table 4**). All-night AHI/ODI as well as AHI/ODI during non-REM and REM sleep significantly predicted diurnal pCO_2 levels. Regression model validity was highest when using REM-ODI as proxy for OSA severity and higher REM-ODI was associated with elevated daytime pCO_2-levels. (**Figure 3**). Mean and lowest overnight saturation were inversely associated with daytime pCO2 and positively correlated with daytime pO2 levels. Associations between sleep apnoea and daytime arterial PO_2 were weaker, only AHI all night and AHI-NREM showed a statistical trend for a negative association. (**Table 4**)

Discussion

Our study, performed at a COPD out-patient clinic, confirmed a high prevalence of OVS. Common predictors of OSA, like the degree of daytime sleepiness, age, or gender did not constitute independent risk factors for OVS in this well-characterized COPD cohort. PAT has proven to be a non-intrusive, easy-to-apply sleep diagnostic instrument feasible for use in a COPD clinic population. On top of conventional polygraphy parameters, the PAT software generates REM-sleep related sleep apnoea measures which appeared to be of clinical relevance. REM-sleep dependent sleep apnoea frequency (AHI) or intermittent hypoxia (ODI) were strong predictors for relevant outcomes like elevated daytime pCO2 levels or increased prevalence of cardiovascular comorbidity.

Several epidemiological studies report an OVS prevalence ranging from below 10% to over 60% in COPD patient cohorts. (4, 29-31) Comparison of results between studies remains challenging because of methodological differences in sleep recording techniques, in study populations, and in OSA- and COPD definitions over time. In fact, recent reviews state the estimated OVS prevalence by 10 to 30% in COPD patients. (2, 32-34) These numbers are in line with the prevalence of OSA identified in the general population suggesting that COPD per se does not predispose to OSA (35). The OVS prevalence of 46% in our data set is in the upper spectrum of the reported OVS prevalence. A potential pre-selection bias towards inclusion of patients with sleep complaints, both from the lung physician and from the patient itself, cannot be excluded in our study design.

To stipulate predictors of OVS provides a challenge as the earlier idea that symptoms of both COPD and OSA are additive has not proven to apply, since sleep related symptoms of OSA like disturbed sleep, daytime sleepiness/fatigue, or waking up with dysponea are often masked by the symptoms of COPD. (3, 34) Pre-selecting of COPD patients for OSA by questionnaires like the ESS or the Berlin questionnaire is hampered by low sensitivity and specificity. (36) A recent study suggests that readily available objective data from medical records, such as age, sex, BMI, and the presence of comorbidities such as systemic hypertension, may be superior to the traditional symptoms of snoring and excessive daytime sleepiness predicting the likelihood of OVS. (37) Our prediction analysis of the OVS diagnosis confirms the fact that classical OSA predictors, with the exception of an elevated BMI, do not fully apply in patients with COPD. A recent meta-analysis compared OVS patients with either COPD or

OSA patients and reported that OVS patients have an increased risk of cardiovascular disease, in particular for systemic and pulmonary hypertension. (38) This is also confirmed in our findings where patients with OVS have a higher prevalence of systemic hypertension, ischemic heart disease, and chronic heart failure compared to patients with COPD alone.

Patients with COPD are at risk to develop hypoxic and hypercapnic respiratory failure and this risk increases gradually with the progressive deterioration of lung function. Previous studies reported that OVS is a predictor for worsened daytime arterial blood gas in relation to compromised pulmonary function. (39, 40) Interestingly, in our study the frequency of sleep-disordered breathing, in particular REM-ODI, was linearly associated with daytime pCO_2 and thereby provided a risk factor for sustained hypercapnia. In contrast, daytime pO_2 levels were not significantly associated with sleep-disordered breathing events.

The burden of OVS during REM sleep is of particular interest but less frequently studied. REM sleep physiology is characterized by muscle atonia including respiratory muscles and reduced ventilatory responses to hypoxic and hypercapnic stimuli. (41) Sleep related hypoxaemia is worsened during REM sleep in OSA alone as well as in OVS. (33) Recent studies showed that REM-related OSA is associated with systemic hypertension (16), metabolic consequences like diabetes mellitus (18), and atherosclerosis. (17) Our study reported – to our knowledge for the first time in OVS patients – that REM-related OSA further increases the likelihood for cardiovascular disease like systemic hypertension and atrial fibrillation. Repetitive sympathetic activation secondary to REM-related OSA may be a potential mechanism behind our finding. (42) However, REM-sleep related OSA have not been analysed in large OVS cohorts probably due to limited access to polysomnographic data in this patient group.

The PAT-based sleep diagnostic method has proven to be feasible (dropout rate <1%), accessible, and tolerable for the patients due to its compact design and the limited number of sensors. When compared to PSG, the gold standard for sleep diagnosis, this technology has shown good agreement in a large number of validation studies performed in patients referred for evaluation of suspected sleep apnoea. (25) One recent study in 500 patients described a larger disagreement between standard PSG and PAT.(43) In this cohort the relation of median AHI3% to median ODI3% events was 18.4 to 2.5 (corresponding PAT-data median AHI3% /ODI4% 25.4/10.9, respectively) suggesting that hypopnea events in PSG were largely scored

due to the arousal criteria without a significant desaturation. This type of respiratory event is less likely to occur in COPD patients because of a generally lower pO_2 level in this patient group leading to desaturation even in mild hypopnoea during sleep. Indeed, several validation studies performed exclusively in COPD patients concluded that PAT detects sleep stages, AHI and ODI in fair agreement with PSG. (22, 23)

Strengths and limitations

Our study included only well characterized COPD patients following a managed care process. Data on lung function, symptomatology, comorbidities and arterial blood gas analysis were of high validity. A referral to the COPD center was not based on symptoms or findings suggestive of OVS. The recruitment process used increases the generalizability of our findings in patients with moderate to severe COPD. The WatchPAT-technology, one of the best validated limited sleep apnoea diagnostic devices in practice, was used in the setting of a COPD care center. The sleep analysis data were based on the automated algorithm without further manual editing. Thereby our study setting reflects the intended use in a COPD center without being dependent on the service of a sleep medicine center during the diagnostic process. Further, the study of Massie et al. compared the reliability of the REM-OSA classification between gold standard polysomnography and a modified PAT-technology (NightOwl) in 261 patients with suspected OSA. (44) The prevalence of REM-OSA was 26.1% in this study which aligns with the 27% prevalence shown in our study. In addition, the authors pointed out that REM-OSA phenotyping by PAT showed lower sensibility but a slightly higher specificity when compared with traditional polysomnography. These findings further strengthen the REM-OSA classification used in our study.

Several study limitations should also be considered. First and most importantly, this was not a study of all consecutive patients seen in the COPD center. As sleep studies were yet not applied in all novel patients as part of a clinical routine, it is likely that patients willing to participate in our study had a higher likelihood of sleep complaints. In addition, the lung specialists in the COPD clinic were also trained in sleep medicine increasing the likelihood to ask the patient for sleep quality and daytime fatigue/sleepiness. Thereby our prevalence data on OVS may be biased towards an overestimation. However, clinical symptoms like daytime sleepiness or snoring history did not predict OVS in previous studies. (45) In addition, COPD patients with already known OSA or treated with home mechanical ventilation were excluded from study participation leading to a potential underestimation of the true OVS prevalence. Second, the sample size of our study is in the medium range for a single-center study and a

formalized sample size calculation was not conducted before study start. In order to get more robust data, in particular for the association between REM related OSA and outcomes like daytime hypercapnia or comorbidities, initiation of large, multi-center clinical cohorts are required to further substantiate our findings. Wide use of the PAT technology in COPD patients may overcome today´s limitation of access to in-lab polysomnography for standard care in COPD patients. Third, the current PAT algorithm does not allow for major manual editing of neither respiratory events nor the calculation of hypoxic burden. One study reported improved agreement between WatchPAT and overnight polysomnography after manual adjustments in the event classification. (46). However, any manual scoring of the PAT recording using indirect information about respiration and sleep stages requires a large experience in scoring of sleep recordings which may usually not be available in the setting of a COPD outpatient clinic. Therefore, our study setting reflects the intended use of the PAT methodology as an add on investigation in the standard care program of COPD patients outside specialised sleep centers.

Clinical consequences and future studies

OVS is common among COPD patients and data suggest a strong association with worsened health outcomes including worsened quality of life, elevated COPD exacerbation frequency, and higher mortality. (32) We suggest that COPD patients should be screened for overlap syndrome as part of the routine clinical practice. In case of limited resources, clinical parameters like male gender, elevated BMI, cardiovascular comorbidity, and elevated pCO2 levels in relation to lung function may strengthen the indication for a sleep evaluation. Snoring witnessed apnoeas and daytime sleepiness may further increase the priority. Simplified sleep test technology, like the PAT used in our study, increases availability for fast track and adequate sleep diagnostics and at the same time taking account for the diagnostic impact of sleep stage dependent sleep apnoea severity. Early detection is vital for COPD patients to reduce disease progression and subsequent mortality.

Future work needs to be directed at identifying disease mechanisms for the prominent role of sleep-disordered breathing during REM sleep in OVS. Diagnostic thresholds for intervention need to be established based on outcome studies. Our data set is very limited with only 49 patients with OVS and 12 patients with REM-related OSA in the OVS group and our important findings need further confirmation in larger COPD patient cohorts.

Conclusion

Our data confirm a high prevalence of OSA in COPD. We documented a strong association between REM-sleep related respiratory events and COPD-relevant outcome like elevated daytime pCO_2 levels and prevalent cardiovascular disease. PAT is a feasible tool for the assessment of OVS in standardized COPD care.

Acknowledgements

The study was supported by grants from the Swedish Heart and Lung Foundation (LG; 20180584, 20180567, 20210529) and the Swedish state under the agreement between the Swedish government and the country councils, the ALF-agreement (LG; 725601 and 966283, LVF; 824371, JH; 966319). We express our gratitude to Monica Crona, research nurse at the COPD outpatient clinic, for excellent patient care and data quality control.

Conflict of interest statements

Ludger Grote reports support from Itamar Medical related to the study (PAT devices and -probes). Outside the scope of the study, he reports lecturing activities for Resmed, Philips, Astra Zeneca, Itamar, and Lundbeck as well as grant support for scientific projects from Desitin and Bayer. He has a co-ownership in a licensed patent for sleep apnoea treatment. Jan Hedner reports support in terms of equipment from Itamar Medical related to the study. Outside the scope of the current study, he reports lecturing activities for Astra Zeneca and Itamar as well as grant support for scientific projects from Desitin and Bayer pharma. He has a co-ownership of a licensed patent for pharmacological sleep apnoea treatment. Anders Andersson reports personal fees outside the submitted manuscript for lectures in pulmonary medicine from Asta-Zeneca, and Boehringer-Ingelheim. Lowie E.G.W. Vanfleteren reports no conflict of interest related to the study. Outside the scope of the study, he reports payment for lectures, advisory boards or consultancy for Resmed, AstraZeneca, GSK, Novartis, Boehringer and Pulmonx. Ding Zou, Kristina Andelid, and Daniel Hansson report no conflict of interest.

Tables and Figures

Table 1. Descriptive statistics over patients included in the study comparing patients with COPD alone vs. OVS-patients.

	Total study population (n = 105)	**OVS (n=49)**	**COPD alone (n=56)**	**Between group statistics (p-value)**
Anthropometric data				
Age, years	68.1±9	70.1±8.2	66.3±9.5	**0.029**
Male gender, %	43.8	55.1	33.9	**0.029**
BMI, kgm^{-2}	28.3±6	30.0±6.4	26.4±6.7	**0.006**
BMI ≥ 25 kgm^{-2} %	70.5	75.5	65.5	**0.290**
Obesity (BMI≥30) %	41.0	52.0	30.9	**0.028**
Systolic blood pressure, mmHg	140.1±16	140.5±17.6	139.7±15.0	0.795
Diastolic blood pressure, mmHg	77.4±12	77.9±12.0	76.9±11.5	0.649
Comorbidities				
Systemic hypertension %	54.2	71.4	44.6	**0.006**
Ischemic heart disease %	16,2	24.5	8.9	**0.031**
Chronic heart failure %	13.3	20.4	7.1.	**0.046**
Atrial fibrilation %	7.6	10.2	5.4	0.350
Stroke %	9.5	2.0	16.1	**0.015**
Diabetes mellitus %	9.5	14.3	5.4	0.120
Malignancy %	16.2	14.3	17.9	0.620
Depression %	26.7	22.4	30.4	0.361
Anxiety %	20.0	20.4	19.6	0.922
Pulmonary function test				

FVC,L	3.1±0.09	2.9±0.9	3.1±0.9	0.296
FEV_1, L	1.51±0.7	1.5±0.7	1.5±0.7	0.778
FEV_1/FVC %	47.4±1.4	48±14	47±14	0.646
COPD severity classification according to FEV_1 (percentage of cohort)				
Stage I, %	1.9	2.1	1.8	N/S
Stage II, %	40.4	39.6	41.1	N/S
Stage III, %	42.3	47.9	37.5	N/S
Stage IV, %	15.4	10.4	19.6	N/S
Arterial blood gases*,				
pH	7.43±0.03	7.42±0.4	7.43±0.03	0.537
pO_2, kpa	9.3±1.5	9.0±1.4	9.6±1.5	**0.029**
pCO_2, kpa	5.2±0.7	5.4±0.7	5.1±0.7	**0.042**
Standard Bicarbonate mmol/L	25.1±2.0	25.4±1.9	24.8±2.1	0.119
SaO_2, %	93.9±2.8	93.2±3.0	94.5±2	**0.018**
Daytime hypoxia <8 kPa, %	17.9	24.4	12.0	0.114
Daytime hypercapnia >6,5 kPa, %	17.5	19.1	16.0	0.684
Symptom assessment				
mMRC	2.5±0.1	2.5±1.2	2.6±1.2	0.748
CAT	21.0±0.7	20.2±1.7	21.8±1.7	0.240
ESS	7.9±0.6	7.7±0.5	8.0±0.5	0.809

Legend: Shown are means and standard variations for continuous variables as well as percentages for categorical variables.

*Analysis performed in 97 patients (50 COPD alone, 47 OVS);

OVS=Overlap Syndrome (COPD plus OSA with AHI≥15n/h); COPD=Chronic Obstructive Pulmonary Disease; BMI=Body Mass Index; FVC=Functional Vital Capacity after bronchodilation; FEV_1=Forced expiratory volume in one second after bronchodilation; pO_2=partial arterial oxygen pressure; pCO_2= partial arterial carbon dioxide pressure; mMRC= medical research council dyspnea scale; CAT=COPD assessment test; ESS=Epworth Sleepiness Scale.

Table 2 – Sleep quality comparing patients with COPD alone vs. OVS-patients presented with between-group statistics.

Parameters	**Total study population (n = 105)**	**OVS (n=49)**	**COPD alone (n=56)**	**Between group statistics (p-value)**
Sleep quality				
Total sleep time, h	6.2±1.7	6.4±1.6	6.1±1.8	0.361
Sleep latency, min	22.7±13.7	20.6±13	24.6±14	0.138
Sleep efficiency %	80.2±10.9	80.6±10.8	79.6±11.0	0.648
Light sleep %	65.8±11.3	66.6±12	65.1±10.5	0.502
Deep sleep %	14.1±6.4	12.7±6.7	15.4±5.9	**0.029**
REM sleep %	20.0±7.2	20.8±6.9	19.3±7.4	0.273
Sleep-disordered breathing				
AHI all-night, n/h	18.4±17.0	30.8±18	7.5±4.0	Used for group definition
AHI REM, n/h	28.3±18.7	41.8±16	15.9±10	**<0.001**
AHI non-REM, n/h	15.2±16.5	25.9±18	5.3±3.0	**<0.001**
AHI supine, n/h	24.1±21.7	39.0±21	9.3±6	**<0.001**
Sleep related hypoxemia				
Mean SaO_2 %	91.5±3	90.6±3	92.3±2	**0.003**
Min SaO_2 %	81.9±8.2	77.2±9	86.0±4	**<0.001**
ODI all-night, n/h	10.2±14.5	18.7±18	2.8±2	**<0.001**
ODI REM, n/h	17.1±16.4	26.9±17	7.9±8	**<0.001**
ODI non-REM, n/h	7.6±13.5	14.1±17	1.7±16	**<0.001**
ODI supine, n/h	14.3±18.7	25.1±21	3.6±3	**<0.001**

Legend: Mean ±standard deviation as well as percentages are shown. OVS=Overlap Syndrome (COPD plus OSA with AHI≥15n/h); COPD=Chronic Obstructive Pulmonary Disease; AHI=Apnoea Hypopnoea Index, ODI=Oxygen desaturation index, REM=Rapid Eye Movement sleep; SaO_2=Oxygen saturation; Min SaO_2 =Nadir of SaO_2 during sleep

Table 3 – Comparison of OVS patients with (n=12) and without (n=33) REM-related OSA presented with between-group statistics.

Parameters	**REM-related OSA (n=12)**	**NREM-related OSA (n=33)**	**Between group statistics (p-value)**
Anthropometric data			
Age, years	68.1±9	70.1±8.2	0.361
Male gender %	43.8	55.1	0.138
BMI, kgm^{-2}	28.3±6	30.0±6.4	0.648
Systemic hypertension %	91.7	63.6	0.069
Ischemic heart disease %	33.3	18.2	0.280
Chronic heart failure %	25.0	15.2	0.445
Atrial fibrillation %	25.0	3.0	**0.022**
Stroke %	0	3.0	0.542
Sleep-disordered breathing			
Total sleep time, h	5.8±0.9	6.8±1.5	0.022
AHI all-night, n/h	19.5±4	32.9±18	**0.002**
AHI REM n/h	46.4±7	40.2±18	**0.03**
AHI non-REM, n/h	11.9±4	30.9±19	**<0.001**
Sleep related hypoxemia			
Mean SaO_2 %	92.5±2.2	90.0±4.0	**0.036**
Min SaO_2 %	79.1±10	77.4±9	0.585
ODI all-night, n/h	10.3±3	19.4±19	0.13
ODI REM, n/h	28.3±8	26.4±20	0.154
ODI non-REM, n/h	4.8±2	17.5±19	**<0.001**

Legend: REM-AHI was not calculated in 4 OVS patients due to short REM-duration. Mean ±standard deviation as well as percentages are shown. OVS=Overlap Syndrome (COPD plus OSA with AHI≥15n/h); AHI=Apnoea Hypopnoea Index, ODI=Oxygen desaturation index, REM=Rapid Eye Movement sleep; SaO_2=Oxygen saturation; Min SaO_2 =Nadir of SaO_2 during sleep.

Table 4.

Sleep apnoea measures as predictors of daytime arterial pCO_2 and pO_2 adjusted for age, gender, BMI and FEV_1.

	pO_2		**pCO_2**	
Variable	Beta-value	P-value	Beta-value	P-value
AHI all night	-0,015	0.086	0.018	**<0.001**
AHI NonREM	-0,016	0.084	0.016	**<0.001**
AHI REM	-0,012	0.189	0.018	**<0.001**
ODI all night	-0,015	0.142	0.022	**<0.001**
ODI NonREM	-0,018	0.119	0.022	**<0.001**
ODI REM	-0,015	0.122	0.022	**<0.001**
Mean SaO_2	0.283	**<0.001**	-0.070	**0.001**
Min SaO_2	0.071	**<0.001**	-0.038	**<0.001**

Legend: AHI=Apnoea-Hypopnoea Index, ODI=Oxygen desaturation index, REM=Rapid Eye Movement sleep; SaO_2=Overnight oxygen saturation; SaO_2 min=Nadir of SaO_2 during sleep.

Abbreviation list

ABG	Arterial blood gases
OSA	Obstructive sleep apnoea
COPD	Chronic obstructive pulmonary disease
OVS	Overlap syndrome (COPD and OSA combined)
AHI	Apnoea hypopnoea index
ODI	Oxygen desaturation index
SDB	Sleep disordered breathing
REM	Rapid eye movement
SD	Standard deviation
IQR	Inter quartile range
BMI	Body mass index
FVC	Forced vital capacity
FEV1	Forced expiratory volume during 1 second
pO_2	Partial pressure of oxygen
pCO_2	Partial pressure of carbon dioxide
mMRC	Modified medical research council dyspnea scale
CAT	COPD assessment test
ESS	Epworth sleepiness scale

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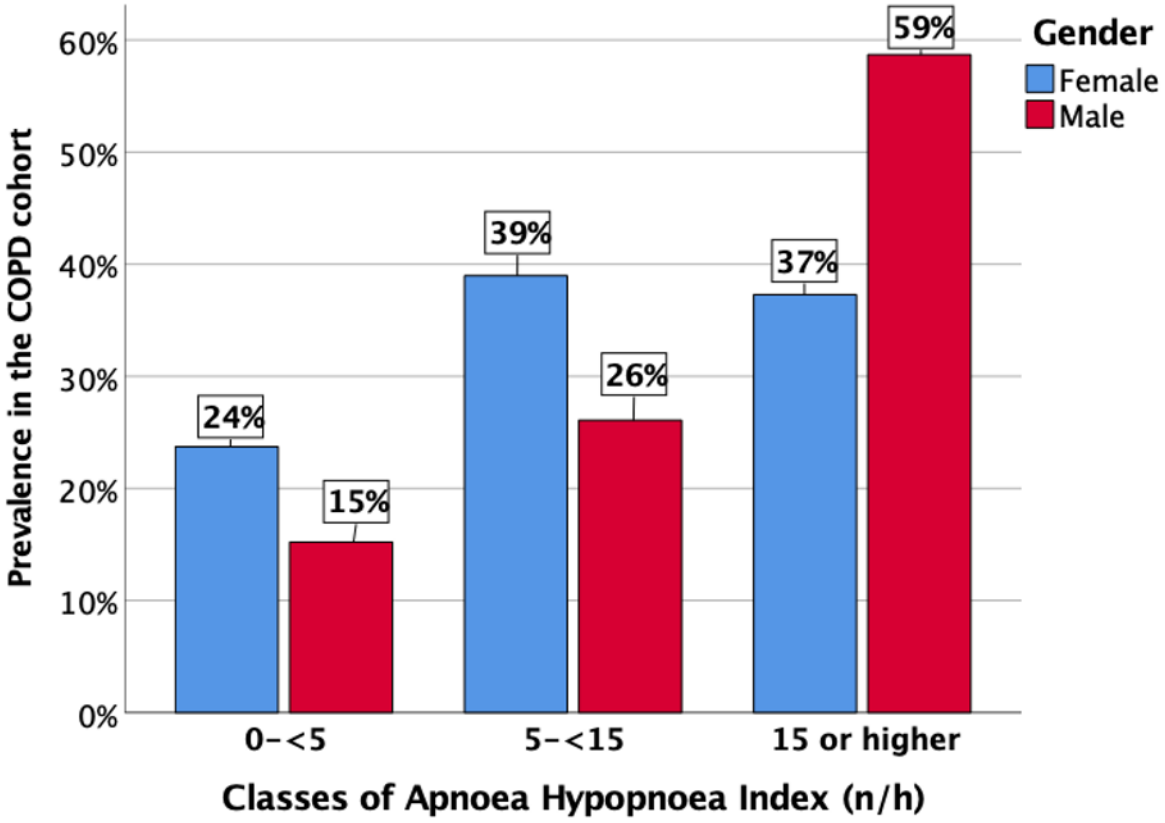
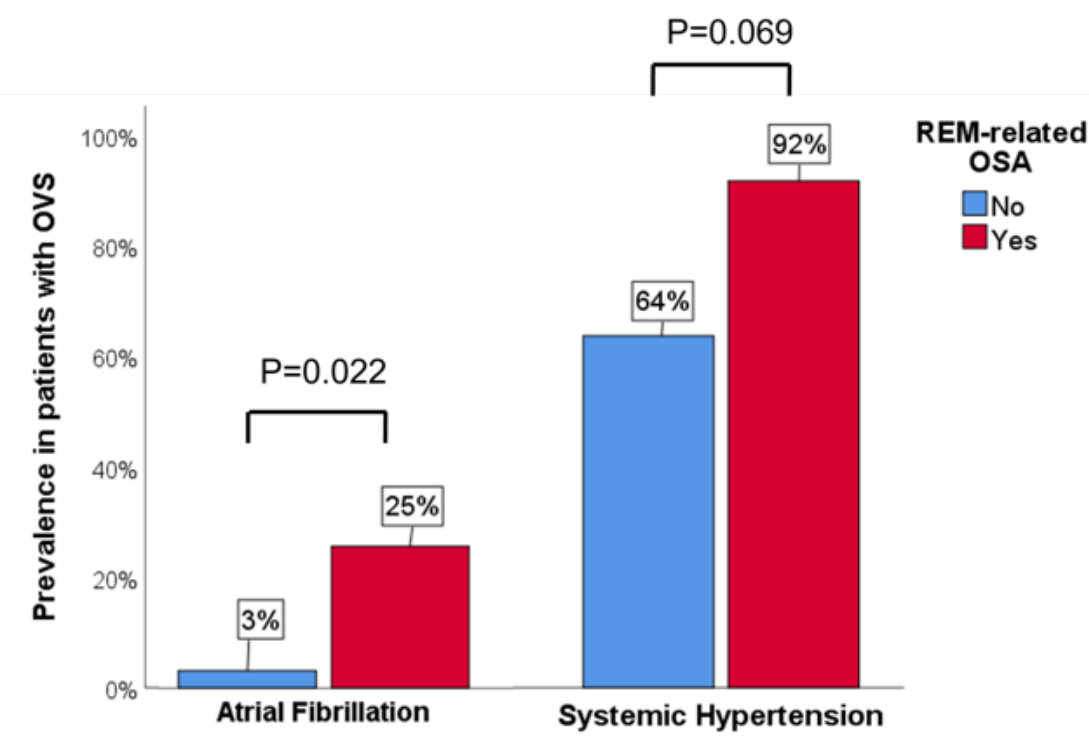
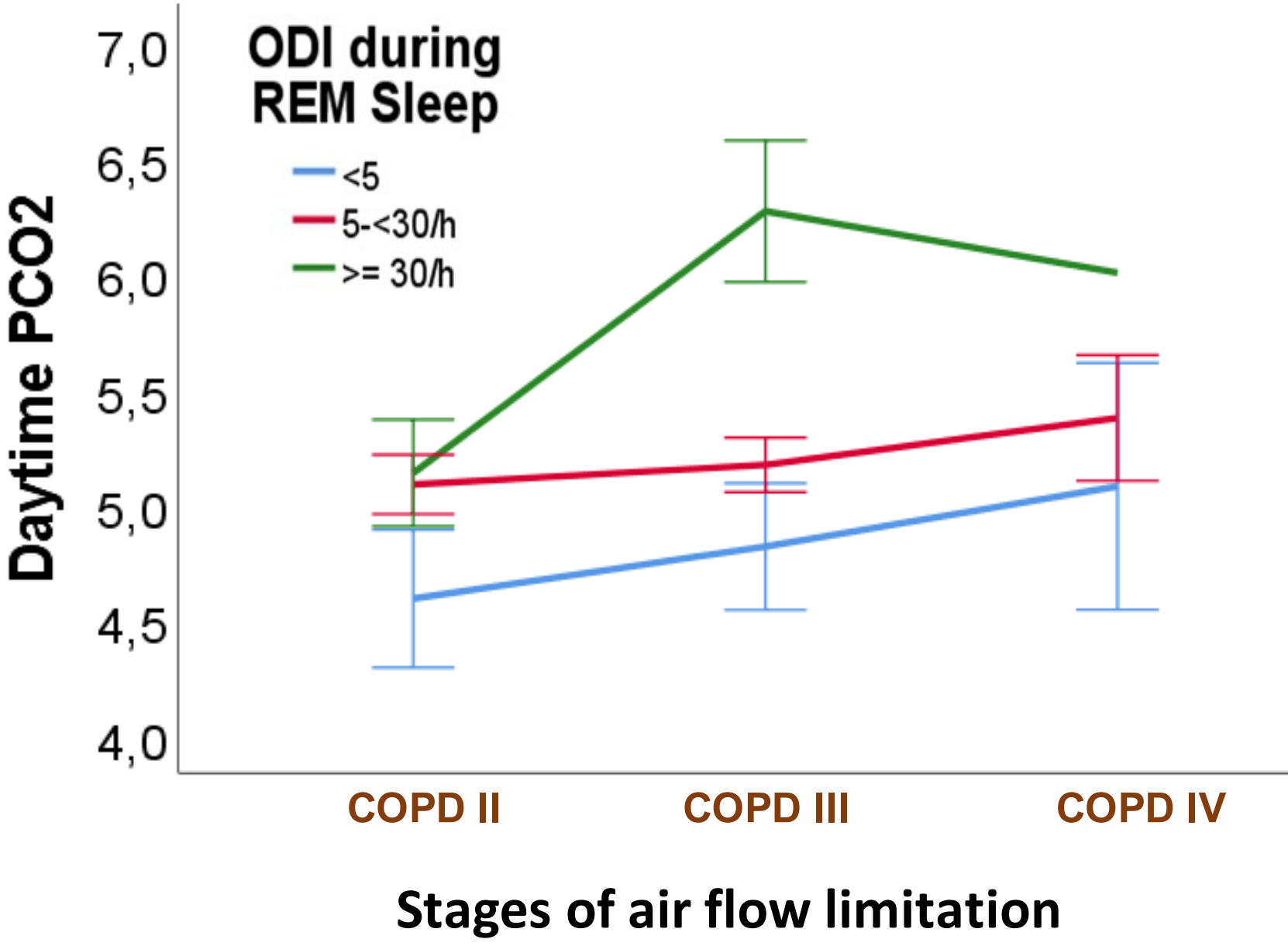

Gender
Female
Male
Prevalence in the COPD cohort
60%
50%
40%
30%
20%
10%
0%
24%
15%
39%
26%
37%
59%
0-<5
5-<15
15 or higher
Classes of Apnoea Hypopnoea Index (n/h)


P=0.069
100%
80%
60%
40%
20%
0%
Prevalence in patients with OVS
92%
64%
P=0.022
25%
3%
REM-related OSA
No
Yes
Atrial Fibrillation
Systemic Hypertension


ODI during
REM Sleep
<5
5-<30/h
>= 30/h
Daytime PCO2
7,0
6,5
6,0
5,5
5,0
4,5
4,0
COPD II
COPD III
COPD IV
Stages of air flow limitation