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Severity of oxygen desaturation in OSA–COPD overlap syndrome compared to OSA alone: an observational cohort study

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Abstract

English:

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) syndrome (OSAS) are both common conditions. Their comorbid association – overlap syndrome (OVS) – can result in clinically important nocturnal oxygen desaturation. We sought to compare demographic and anthropometric characteristics, associated comorbidities and oxygen saturation in patients with OVS versus OSA alone.

***Methods:** We included consecutive patients diagnosed with OSA in our sleep laboratory. Overnight sleep studies were performed, and data regarding demographic and anthropometric characteristics, prevalence of comorbidities and somnographic parameters were compared for patients with OVS versus OSA alone. A P value of <0.05 was considered significant.*

***Results:** A total of 2173 OSA patients were assessed, of whom 381 (17.5%) had OVS. Significant differences were found between the OVS and OSA groups regarding all evaluated demographic and anthropometric characteristics, prevalence of comorbidities and somnographic parameters.*

***Conclusions:** OVS patients were older, were predominantly male, had a higher prevalence of common cardiovascular and metabolic comorbidities, and had worse apnoea–hypopnoea index (AHI) and oxygen saturation parameters.*

Keywords

overlap syndrome • sleep apnoea • oxygen desaturation • comorbidities

Severitatea desaturarilor in oxigen in sindromul overlap SAS-BPOC comparativ cu SAS: studiu observational de tip cohorta

Rezumat

Romanian:

Boala pulmonară obstructivă cronică (BPOC) și sindromul de apnee în somn de tip obstructiv (SAOS) sunt afecțiuni cronice iar asocierea lor - sindromul „overlap" (OVS) poate duce la desaturări clinic importante pe timpul nopții. În lucrarea prezentă s-au comparat caracteristicile demografice și antropometrice, comorbiditățile asociate și saturația oxigenului la pacienții cu OVS versus cei cu SAOS. Au fost incluși pacienți diagnosticați cu SAOS în laboratorul nostru de somnologie. Au fost efectuate poligrafii nocturne și s-au colectat date privind caracteristicile demografice și antropometrice, prevalența comorbidităților și parametrii somnografici de la pacienții cu OVS și cei doar cu SAOS. Un valoare P < 0,05 a fost considerat semnificativă.

***Rezultate:** Au fost evaluați 2173 de pacienți cu SAOS, dintre care 381 (17,5%) au avut OVS. S-au găsit diferențe semnificative între grupurile OVS și SAOS cu privire la toate caracteristicile demografice și antropometrice evaluate, prevalența comorbidităților și parametrii somnografici.*

***Concluzii:** Statistica noastră a arătat că pacienții cu OVS sunt mai în vârstă, de sex predominant masculin, au o prevalență mai mare a comorbidităților cardiovasculare și metabolice și au valori mai mari ale AHI precum și valori mai mici ale saturației în oxigen.*

Cuvinte-cheie

sindrom overlap • apnee in somn • desaturari in oxigen • comorbiditati

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Introduction

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) syndrome (OSAS) are both common conditions and among the most prevalent chronic respiratory disorders (1). GOLD (2020) defines COPD as a preventable and treatable disease characterised by persistent respiratory symptoms and airflow limitation that is usually progressive and associated with exposure to noxious particles or gases, especially smoking (2). In most patients, COPD is associated with significant chronic diseases, which increase its mortality and morbidity (2). On the other hand, OSA is defined by the presence of intermittent collapse of superior airways during sleep that leads to recurrent hypoxia, sleep fragmentation and daytime sleepiness (3).

Coexistence of these two pathologies in the same patient was first described by Flenley in 1985 using the term overlap syndrome (OVS) (4). OVS has a prevalence of approximately 1% in the general population, and it has been associated with poor quality of life, higher prevalence of metabolic and cardiovascular comorbidities and a higher risk of respiratory exacerbation (5). Patients with OVS have higher mortality than those with COPD alone, and the adverse effects of COPD and OSA may be synergistic rather than additive (6). As some studies have shown, 29%–85% of the patients with COPD are also diagnosed with OSAS (7).

COPD alone can cause subjective and objective changes during sleep. Specifically, patients with COPD report difficulty in both initiating and maintaining sleep and also complain of excessive daytime sleepiness. More than just the diagnosis of COPD, the presence of COPD symptoms, such as cough, sputum production or wheezing, is strongly correlated with difficulty in falling or staying asleep (8). Other studies have confirmed poor sleep quality, with decreased total sleep time and decreased sleep efficiency. The most significant sleep abnormality associated with 27%–70% of patients with COPD is nocturnal oxygen desaturation (time below oxygen saturation limit, such as 90%) (9).

Materials and methods

We conducted an observational cohort study on two groups of patients – patients diagnosed with OVS versus patients diagnosed with OSA – in order to evaluate demographic and anthropometric characteristics, associated comorbidities and oxygen saturation parameters. Consecutive patients diagnosed with OSA between 2005 and 2018 in the sleep laboratory of the Infectious Diseases and Pulmonology Hospital 'Dr. Victor Babeș', Timisoara were enrolled in our study. Clinical data on the presence of several associated chronic diseases were systematically collected from all patients, based on patients' self-reporting of concomitant conditions, medication use and available medical records. Also, parameters such as height, weight, neck circumference, hip and waist circumference, waist-to-hip circumference ratio and body mass index (BMI) were measured as part of a clinical examination.

The diagnosis of COPD was established according to standard diagnostic criteria: chronic symptoms, such as dyspnoea, cough and sputum production, combined with exposure to risk factors and an obstructive ventilatory dysfunction with an FEV1/FVC ratio of less than 0.7 showing during functional respiratory exploration conducted through spirometry (10).

All patients enrolled in the study underwent an attended somnography. The respiratory events were assessed using nasal thermistors and thoracic/abdominal strain gauges, while oxygen saturation was monitored using a pulse oximeter placed on the index finger of the non-dominant hand. Apnoea was defined as ≥90% reduction in airflow for at least 10 s, while hypopnoea was defined as ≥30% reduction in airflow for at least 10 s in combination with an oxygen desaturation of at least 3% (11). The diagnosis of OSAS was established if the apnoea–hypopnoea index (AHI) was ≥15/hr in an asymptomatic patient, or ≥5/hr in a patient with symptoms or signs of disturbed sleep, and more than 75% of the apnoeas and hypopnoeas must have been obstructive (11).

Once all the data were obtained, these were used to stratify the patients into the two groups of OSA and OVS, and the characteristics of the two groups were then compared, with these data as the basis using the chi-square or Mann–Whitney test (depending on the type of variables). Data distribution was not normal, and therefore, we report the median values (interquartile range [IQR]). Statistical significance was defined at 5% ($P < 0.05$). The results are presented as graphs, tables and diagrams and are expressed as absolute numbers and percentages.

Results

The study population consisted of 2173 patients (71.2% males), of whom 381 (17.5%) had OVS and 1792 patients (82.5%) had OSA alone. Significant differences between the OVS and OSA groups were found with respect to demographic and anthropometric characteristics, as presented in Table 1.

As we can observe, the majority of patients in both groups were males; however, the male predominance was significantly higher in the OVS group than in the OSA alone group. Patients in the OVS group were older (58.0 vs 53.0,

Table 1. Comparison of anthropometric characteristics between patients with OVS and patients with OSAS

Characteristics	OVS *N* = 381	OSA *N* = 1792	*P* value
Age (years) – median value (IQR)	58.0 (13)	53.0 (18)	<0.001*
Gender – male	83.5%	68.6%	<0.001**
BMI (kg/m^2) – median value (IQR)	35.1 (9.4)	32.0 (8)	<0.001**
Neck circumference (cm) – median value (IQR)	46.0 (5)	43.0 (6)	<0.001**
Waist-to-hip ratio – median value (IQR)	1.03 (0.09)	0.99 (0.9)	<0.001**

BMI, body mass index; IQR, interquartile range; OSA, obstructive sleep apnoea; OSAS, obstructive sleep apnoea syndrome; OVS, overlap syndrome.
*Chi-square test.
**Mann–Whitney test.

Table 2. Prevalence of comorbidities in patients with OVS compared with patients with OSAS

Comorbidities	OVS *N* = 381	OSA *N* = 1792	*P* value
Arterial hypertension	79.5%	66.9%	<0.001*
Coronary artery disease	49.2%	28.9%	<0.001*
Arrhythmias	30.8%	22.7%	<0.001*
Diabetes mellitus	38.1%	17.4%	<0.001*
Obesity	81.6%	66.9%	<0.001*
Stroke	5.8%	4.3%	0.222*

OSA, obstructive sleep apnoea; OSAS, obstructive sleep apnoea syndrome; OVS, overlap syndrome.
*Chi-square test.
*Mann–Whitney test.

Table 3. Somnographic characteristics of patients with OVS versus patients with OSAS

Somnographic characteristics	OVS *N* = 381	OSA *N* = 1792	*P* value
AHI (events/hr)	44.2 (37.5)	40.2 (36.9)	0.011*
ODI	30.7 (46.5)	21.6 (39.3)	<0.001*
Mean oxygen saturation (%)	91.0 (6)	94.0 (4)	<0.001*
Lowest oxygen desaturation (%)	77.0 (17)	80.0 (15)	<0.001*
Duration of longest desaturation (s)	2.5 (15.4)	1.3 (13.8)	0.013*

AHI, Apnea–hypopnea index; ODI, Oxygen desaturation index; OSA, obstructive sleep apnoea; OSAS, obstructive sleep apnoea syndrome; OVS, overlap syndrome.
*Mann–Whitney test.

P < 0.001) and had a significantly higher BMI (35.1 vs 32.0, *P* < 0.001). We can also remark that the mean value of the neck circumference and waste-to-hip ratio was higher in patients with OVS compared with patients with OSA (in both cases, the *P* value was less than 0.001).

In addition, we have also found significant differences between the OVS and OSA groups in terms of the prevalence of several conditions. In both groups, arterial hypertension was the most prevalent comorbidity (79.5% for OVS vs 66.9% of OSA, *P* < 0.001), followed by obesity (81.6% for OVS vs 66.9% of OSA, *P* < 0.001) and coronary artery disease (49.2% for OVS vs 28.9% of OSA, *P* < 0.001). A great percentage of the patients were having different arrhythmias (30.8% in OVS group vs 22.7% in OSA group, *P* < 0.001). Another metabolic comorbidity, diabetes mellitus, was more prevalent in patients with OVS than in patients with OSA (38.1% vs 17.4%, *P* < 0.001). Although there was no statistical significance, a high percentage of patients from the OVS group reported having a stroke in the past (5.8% in OVS vs 4.3% in OSA, *P* = 0.222). Table 2 presents the most prevalent conditions that were found in OVS and OSA patients during our study.

Last but not least, Table 3 presents a comparison of the AHI and oxygen saturation parameters in the two groups after interpreting the somnography results of all patients enrolled in the study.

The mean AHI was in the range of severe OSA for both groups; however, patients in the OVS group had a significantly higher AHI (44.2 vs 40.2, *P* = 0.011). Furthermore, all of the measured oxygen saturation parameters were lower in the group of patients with OVS than in the group of patients with OSA alone. The oxygen desaturation index (ODI) was 30.7 in the OVS group versus 21.6 in the OSA group (*P* < 0.001); the mean value of oxygen saturation was lower in patients with OVS, at 91.0, against 94.0 in the OSA group (*P* < 0.001); and the lowest oxygen saturation was 77.0 in patients with OVS versus 80.0 in patients with OSA (*P* < 0.001), while the duration of longest desaturation was twice as high in OVS patients, 2.5 s., than in patients with OSA alone, 1.3 s (*P* = 0.013).

Discussion

The present study highlights important findings in the field of OVS. Firstly, patients from the OVS group are predominantly male, are older, are more obese and have a larger neck circumference and waist-to-hip ratio compared with patients with OSA alone. Secondly, our study demonstrates that most of the patients diagnosed with OVS have an increased number of concomitant diseases, especially cardiovascular diseases, and their prevalence is higher compared with patients

with OSA alone. Finally, when comparing somnographic parameters of patients in both categories, we observe worse oxygen saturation indices, with more severe episodes of OSA and nocturnal hypoxemia, in the OVS group.

In 2018, a similar study was carried out that assessed two groups of patients – 38 patients with OVS versus 38 patients with OSA only, according to demographic and anthropometric characteristics, prevalence of cardiovascular comorbidities and the somnographic indices; the results were comparable with those of our study – cardiometabolic diseases (hypertension, cardiovascular disease, type 2 diabetes and dyslipidemia) were more frequent in patients with OVS; however, the difference between the number and/or the type of comorbidities did not reach a statistically significant level. Patients from the OVS group had lower oxygen saturation, but there was no difference in terms of age, BMI and neck, waist and hip circumference between the two groups (12). This is in line with our findings that patients with OVS had a higher prevalence of arterial hypertension and obesity. We were able to demonstrate more significant differences between OVS and OSA patients, probably because of a considerably higher patient population.

A recent study conducted on an Asian population showed that daytime hypoxemia and hypercapnia can also contribute to the development of cardiovascular diseases (13). Hypoxemia is thought to act as a cardiovascular risk factor by increasing cardiac load, inducing oxidative stress by concomitant release of reactive oxygen species, impairing vascular endothelial function and causing electrophysiological instability in the cardiac conduction system (13). Chronic hypoxia and hypercapnia caused by COPD and intermittent nocturnal hypoxia caused by OSA can lead to a decrease in the sensitivity of the respiratory centre to both hypoxemia and hypercapnia stimulation in patients with OVS, leading to further worsened hypoxemia and hypercapnia. Moreover, this study showed that patients with overlap had higher levels of daytime hypoxemia and hypercapnia, as well as a higher prevalence of heart failure and pulmonary arterial hypertension, than the COPD or OSA groups. Therefore, together with nocturnal hypoxemia, daytime hypoxemia and hypercapnia may have a synergistic effect on promoting cardiovascular diseases (13).

An important factor in cardiovascular disease may be the expression of systemic inflammatory mediators that are worsened by hypoxia and lead to systemic inflammation (13). There are many common molecular signalling pathways between COPD and OSA, such as C-reactive protein, interleukin 6 and nuclear factor kappa B. Their interaction can cause a systemic inflammatory response and increased body oxidative stress, leading to cardiovascular diseases (13). On the other hand, nocturnal hypoxia and sleep fragmentation could activate the sympathetic system and the hypothalamus–pituitary–adrenal axis, trigger low-grade inflammation, oxidative stress and endothelial dysfunction and promote insulin resistance (12).

Another study that enrolled 1887 patients suspected with OSA, of whom 62.1% were diagnosed with OSA, showed that OSA severity was associated with higher prevalence of heart attack, coronary artery disease, hypertension, diabetes and obesity (14). Regarding the connection between OSA and COPD, a study was conducted in Warsaw to evaluate a possible epidemiological relationship between OSA and COPD in a random population sample; 11.3% of patients were diagnosed with OSA and 10.7% with COPD, while in 1% of the studied population, OSA and COPD overlapped (15). Moreover, in the group of patients with OVS, the mean arterial blood saturation and time spent in desaturation were lower than the corresponding values from the OSA group, suggesting a more severe course of sleep-disordered breathing in subjects with coexisting COPD (15).

In the research carried out on a Swiss, cross-sectional study population (16), it was ascertained that almost 20% of the enrolled patients had COPD, and that in the middle-aged general population, the prevalence of OSA with only mild symptoms might extend up to 30%; those meeting the latter criteria, after the performance of a spirometry examination, were accordingly categorised in COPD GOLD stages I–IV. As our study showed, patients with OVS were predominantly males, were older, were more obese and had more associated comorbidities compared with patients who had COPD only (16).

Certainly, our study is subject to several limitations. Firstly, there was a lack of data on patients' medical history, including lifestyle conditions, risk factors, etc., which could have influenced our results. Also, we could not correctly evaluate the presence of daytime hypoxemia and hypercapnia, while we did not perform an analysis of arterial blood gases. Insufficient follow-up data of the studied population represents another limitation characterising our study. Finally, we should have had ideally assessed another control group of patients with COPD alone for more extensive data on lung function impairment, COPD symptoms and exacerbations, inhaled treatment, compliance, etc. Therefore, in order to enable an assessment of the general and specific characteristics of this particular population of patients associating OSA and COPD, further evidence collection, especially in relation to parameters such as polysomnography events, comorbid diseases and mortality, is indispensable (17).

Conclusions

To conclude, our study confirms that OVS is associated with worse oxygen saturation indices and a higher prevalence of cardiovascular and metabolic comorbidities compared with

OSA alone. The concomitant presence of COPD and OSA in the same patient seems to be more than just a simple association. Identification of an OVS in OSA or COPD patients may have practical clinical relevance as positive airway pressure therapy in OSA patients with COPD can improve overnight oxygen saturation and survival.

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Author's contributions

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Conflict of interest

The authors declare no conflict of interest.

Institutional review board statement

The study was conducted according to the Declaration of Helsinki's guidelines and approved by the local Ethical Commission, 'Victor Babes' University of Medicine and Pharmacy, Timisoara on 24 July 2019, No. 22/2014/24.07.2019.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

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