2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Sleep Apnea & Chronic Obstructive Pulmonary Disease: Overlap Syndrome Dynamics in Patients from an Epidemiological Study

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Abstract— **Obstructive sleep apnea (OSA) is a sleep disorder in which repetitive upper airway obstructive events occur during sleep. These events can induce hypoxia, which is a risk factor for multiple cardiovascular and cerebrovascular diseases. Chronic obstructive pulmonary disease (COPD) is a disorder which induces a persistent inflammation of the lungs. This condition produces hypoventilation, affecting the blood oxygenation, and leads to an increased risk of developing lung cancer and heart disease. In this study, we evaluated how COPD affects the severity and characteristics of OSA in a multivariate demographic database including polysomnographic signals. Results showed SpO2 subtle variations, such as more non-recovered desaturations and increased time below a 90% SpO2 level, which, in the long term, could worsen the risk to suffer cardiovascular and cerebrovascular diseases.**

Clinical Relevance— **COPD increases the OSA risk due to hypoventilation and altered SpO_2 behavior.**

I. Introduction

Obstructive sleep apnea (OSA) is a sleep disorder that induces an involuntary total or partial occlusion of the upper airways. This occlusion is responsible for a reduction of the respiratory flow and induces the appearance of hypoxic events. It is a highly prevalent disease estimated to affect between 9% and 38% of the adult population [1], and related to an increased risk of cardiovascular and cerebrovascular diseases [2]. Chronic obstructive pulmonary disease (COPD) induces a persistent inflammation of the lungs causing an obstruction of the air pathways. This condition causes hypoventilation, which results in lower blood oxygen levels and an increased difficulty to breathe. It is also a highly prevalent disease, estimated to affect from 7% to 27% of adult population [3].

The OSA-COPD overlap syndrome is the presence of both conditions at the same time, and it is expected to affect, at least, 1% of the general population [4]. There have already been different attempts to study this overlap syndrome, which determined a variety of worsened consequences, such as the presence of hypoventilation during rapid eye movement (REM) sleep [5], the tendency of OSA-COPD patients to avoid sleeping in supine position [6] or the increased apnea hypopnea index (AHI) due to the increased occurrence of microarousals [7]. Nevertheless, one of the major issues in studying the effect of this comorbidity relies on the difficulty to obtain COPD patients willing to perform a polysomnography (PSG), which is the gold-standard technique to diagnose OSA and other sleep disorders. This issue is even more noticeable in patients with more severe COPD, in whom the use of long-term oxygen therapy complicates the assessment of the effects of COPD on OSA.

Due to the difficulty to assess the OSA-COPD overlap syndrome, and due to the variety of consequences found in multiple different research studies, in this paper we propose to analyze the effects of the OSA-COPD overlap syndrome in patients from an epidemiological database, which allowed us to analyze a large number of OSA-COPD patients.

II. Materials and Methods

A. Database

The database used in this study was provided by the Medical Faculty at the Ernst Moritz Arndt University of Greifswald under the reference number "SHIP/2019/139/D". It consists of a population-based epidemiological study in the region of Pomerania (Germany) known as "Study of Health in Pomerania" (SHIP). The SHIP database aims to include the investigation of health in all its aspects and complexity, which involves the collection and assessment of data relevant to the prevalence and incidence of population-relevant diseases and their risk factors.

B. OSA & COPD Assessment

The OSA severity (Table 1) was determined from the SHIP database containing sleep and respiratory scoring results based on a PSG. The COPD condition was determined using the spirometry information from the SHIP database according to the table 1 from the "Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease" guidelines [8]. A subject was classified as control if the ratio FEV1/FVC was greater or equal to 0.7, and COPD otherwise. If a subject was classified as COPD, a second subclassification in the categories GOLD 1 to GOLD 4 was also performed to determine the COPD severity. This subclassification was based on the predicted FEV1 obtained

* This work was supported in part by the "La Caixa" Foundation (ID 100010434) under fellowship codes LCF/BQ/DI17/11620029 and LCF/BQ/DE18/11670019, in part by the European Union's Horizon 2020 Research and Innovation Program under the Marie Sklodowska-Curie Grant number 713673; in part by the CERCA Program/Generalitat de Catalunya, in part by the Secretaria d'Universitats i Recerca de la Generalitat de Catalunya under grant GRC 2017 SGR 01770; in part by the Spanish Ministry of Science, Innovation and Universities under grant RTI2018-098472-B-I00 MCIU/AEI/FEDER, UE.

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by the equations from the study from Hankinson et al. on spirometric reference values from general U.S population [9].

C. Inclusion and Exclusion criteria

All the subjects from the database were used for this study. The inclusion criteria were those used by the owners of the SHIP database for their epidemiological study [10]. The exclusion criteria used to discard subjects was based upon two main aspects: the availability of spirometry data to be able to determine the COPD condition, and the availability of PSG data to assess the OSA condition. Subjects which did not have data for either one of those conditions were excluded from the study.

D. Features Analyzed

For each subject in the database, the following variables were extracted from the PSG and compared versus the control group with a Mann-Whitney-Wilcoxon statistical test:

- Oxygen saturation (SpO_2) variables: number of desaturations, oxygen desaturation index (ODI), median duration and depth of the desaturations, percentage of time below 90% (CT90) and 95% (CT95), median basal level without considering desaturations, and percentage of desaturations that did not recover the basal level prior to the onset of desaturation in a 2-minute time window.
- Position variables: percentage of time sleeping in supine position and number of position transitions during sleep.
- Event-related variables: number and percentage of events which are apneas or hypopneas, percentage of central apneas within all apneas and number of microarousals.

III. Results

Table I shows a summary of the subjects of the database, including the number of subjects, age, Body Mass Index (BMI) and AHI in each category separated by sex. The percentage of subjects with mild, moderate, and severe OSA is also indicated. The database is balanced regarding, age, BMI, and AHI between the different categories, but it is unbalanced regarding the number of subjects between the control and COPD categories. Yet, this unbalanced number of subjects matches the prevalence of COPD in the general population. It is also noticeable that there are no severe COPD subjects (GOLD 4) in the database.

TABLE I. Database Description

	Categories				
	Control	***COPD***	***Gold1***	***Gold 2***	***Gold 3***
Subjects	952	78	39	33	6
Female	453	24	14	9	1
Male	499	54	25	24	5
Female age ($\bar{x} \pm$ std)	54 ± 13	56 ± 12	52 ± 11	62 ± 10	74 ± 0
Male age ($\bar{x} \pm$ std)	53 ± 14	55 ± 14	50 ± 16	59 ± 11	58 ± 12
Female BMI ($\bar{x} \pm$ std)	28 ± 5	27 ± 7	28 ± 9	27 ± 4	25 ± 0
Male BMI ($\bar{x} \pm$ std)	29 ± 4	27 ± 5	27 ± 5	28 ± 5	29 ± 3
Female AHI ($\bar{x} \pm$ std)	7 ± 9	7 ± 9	5 ± 7	11 ± 12	1 ± 0
Male AHI ($\bar{x} \pm$ std)	12 ± 13	13 ± 14	11 ± 13	15 ± 16	10 ± 6
% subjects mild OSA	27	22	18	21	50
% subjects moderate OSA	16	21	15	27	17
% subjects severe OSA	7	8	5	12	0

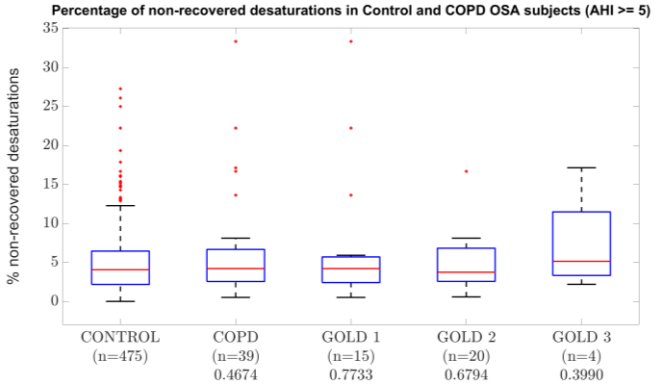

Figure 1. Boxplot of the percentage of non-recovered desaturations in non-healthy OSA subjects (AHI>=5) separated by five categories: Control, COPD, GOLD 1, GOLD 2 and GOLD 3. For each category, the number of subjects available (n) is provided.

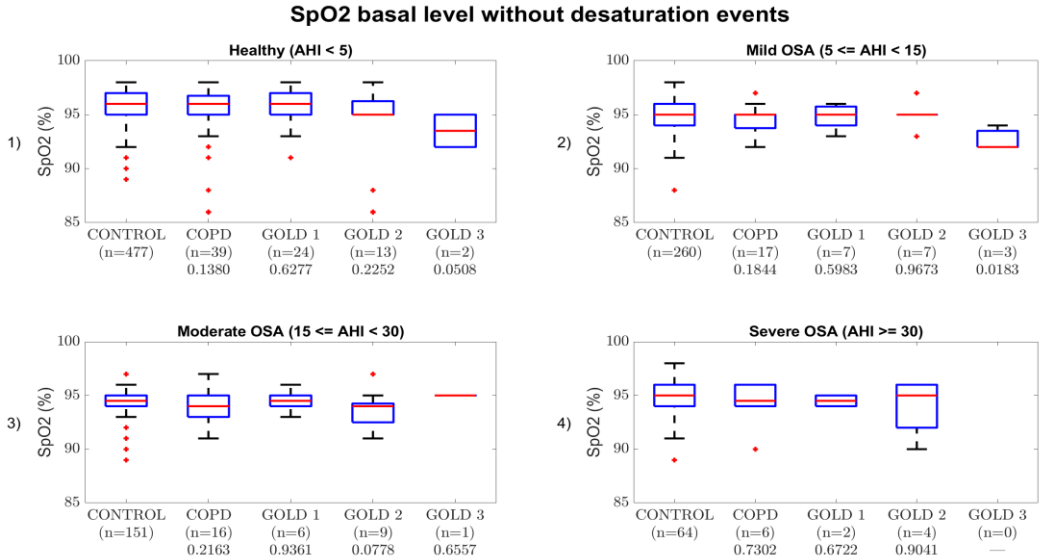

Figure 2. Boxplot of the full-night SpO_2 median basal level, excluding desaturation events, and separated by the four AHI severity groups. For each group, five categories are provided: Control, COPD, GOLD1, GOLD2 and GOLD3. For each category, the number of subjects available (n), and the p-value obtained from the Mann-Whitney-Wilcoxon statistical test vs the control group are provided.

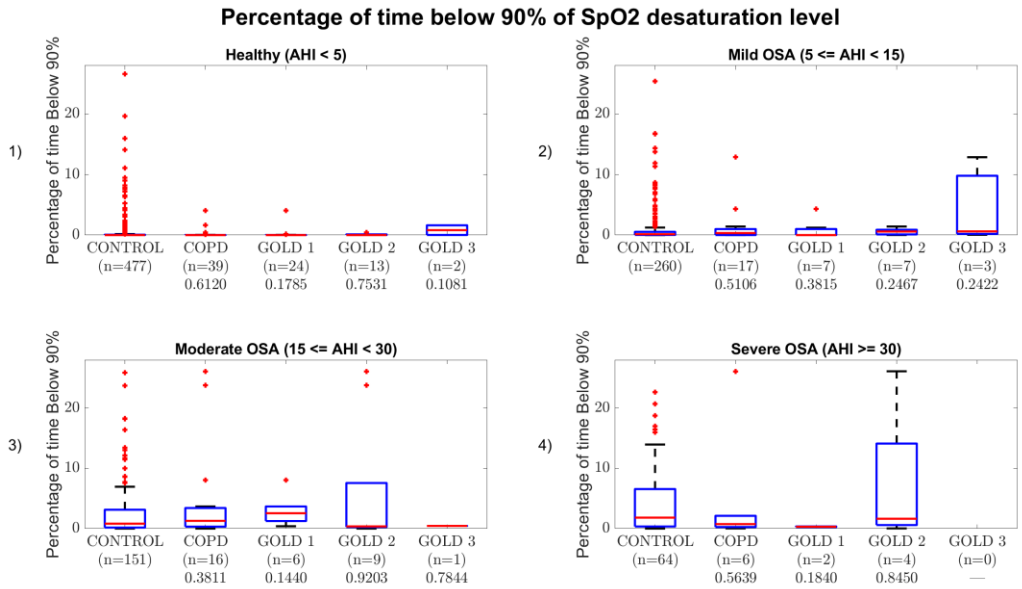

Figure 3. Boxplot of the percentage of time below a 90% SpO2 level and separated by the four AHI severity groups. For each group, five categories are provided: Control, COPD, GOLD1, GOLD2 and GOLD3. For each category, the number of subjects available (n), and the p-value obtained from the Mann-Whitney-Wilcoxon statistical test vs the control group are provided.

Regarding the features analyzed in the database, Fig. 1 shows the percentage of non-recovered desaturations for each of the four categories of the database, excluding subjects with AHI<5. This figure shows how this percentage slightly increases with COPD severity, indicating that, in these subjects, more desaturations are not recovering the basal level prior to the onset of the desaturation in a two-minute time window from the start of the desaturation.

In Fig. 2 it is possible to observe the median basal SpO_2 value during the night excluding the moments where a desaturation occurred. It is possible to observe how the SpO_2 median value is lower for the COPD categories when compared to the control. In these category comparisons, almost none of the statistical tests reported a significance difference (p value < 0.05), even though the GOLD 2 category was significantly different from the mild group and almost from the healthy and moderate groups. It is also noticeable how the median basal value slightly decreases when moving from the healthy to the severe groups.

In Fig. 3 the percentage of time of the whole night below a 90% of SpO2 value can be seen. This figure shows how this percentage increases with the OSA severity, but it also slightly increases with the COPD severity. However, the statistical tests for these category comparisons did not report significant differences.

Finally, regarding all the other features analyzed from the database, most of them had a similar behavior than the features shown in Fig. 1-3. For instance, subtle differences were observed in apnea duration, with slightly higher apnea duration times in the COPD category compared to the control (median: 23.14 vs 21.66 s). The same behavior was seen in hypopneas (median: 29.54 vs 28.33 s), but with a smaller difference in increased duration time between COPD and control groups. Regarding the sleep position, subtle lower percentages of supine sleep position were also observed in the COPD category when compared to the control (median: 43.88% vs 47.08%). All these features did not yield statistically significant differences between them, even though the same pattern of subtle worst conditions were shared among these comparisons.

IV. Discussion

A. Epidemiological Database outcome

The epidemiological SHIP database can provide a relevant solution to one of the main problems when aiming to study the OSA-COPD overlap syndrome, which is the availability of patients who underwent PSG. Since hospital units performing PSGs usually determine the sleep quality by assessing OSA through the determination of the AHI index, the effect of some comorbidities is usually not analyzed, and thus remains unknown and unavailable. Besides, sometimes the hospital department in charge of performing the PSG is different from the department managing COPD, and the interaction between departments can be physically or bureaucratically unavailable. For this reason, having the opportunity to analyze the SHIP database was very useful to obtain enough COPD patients to determine sleep patterns.

Regarding the information in the database, in Table I we can observe that there were no GOLD 4 subjects available. To understand this situation, we must take into consideration that the most severe COPD patients are usually in long term oxygen therapy, and the management of these patients to perform a PSG is complicated. For this reason, it is likely that most severe COPD patients were excluded from the sleep tests performed in the epidemiological database. In addition, we can notice that the prevalence of COPD within the database is of 7.6%, which agrees with the prevalence of COPD in the general population [3]. This situation led us with an unbalanced database, with around twelve more times control patients than COPD patients, but, at the same time, reflects the reality of the presence of COPD in the population, which is important for its analysis.

Finally, despite the differences in the number of patients between the control and the COPD category, we can observe that the database is fairly balanced in terms of age, BMI and AHI. Regarding sex, the number of subjects per category is not balanced in the COPD categories, but except GOLD 3, all the other categories have enough individuals to compare them. In addition, the percentage of mild, moderate, and severe OSA subjects is balanced, which allows to determine patterns in each of the four OSA severity groups.

B. OSA-COPD overlap syndrome

The novel analysis performed in this study revealed subtle differences in the COPD subjects compared to the control group. These subtle differences were, in most cases, non-significant according to the Mann-Whitney-Wilcoxon statistical test. Nevertheless, it is important to consider that no GOLD 4 subjects were included, for which a more significant variation would be expected. This idea is reinforced when understanding that the sleep tests are performed in a resting scenario where the COPD condition is not stressed, and, for this reason, less severe COPD subjects tend to perform more equally to the control group, whereas more severe subjects would be expected to report more differences.

Regarding the subtle differences observed, it is important to remark the concept that COPD patients would have more difficulties to recover a healthier SpO_2 basal level when compared to the control group. This idea can be seen in Fig. 1, where COPD subjects had more non-recovered desaturations, Fig. 2, where the SpO_2 basal level in COPD subjects is lower than the control group, and Fig. 3, where the percentage of time below 90% SpO_2 value is higher in COPD subjects. This situation is stressed when apneas and hypopneas occur, which slightly emphasizes the COPD condition. In those figures, multiple outliers appear for the control category. We consider that these outliers could be related to other comorbidities (e.g. asthma) affecting the control group. In future studies, we will deepen in determining these other comorbidities to observe their effect vs COPD.

C. Short-term vs Long-term symptoms and consequences

An important aspect to consider in sleep studies is the impact that a condition might have on its short-term or long-term consequences. Sleep apnea has multiple symptoms which have short-term consequences, such as feeling tired, morning headache or sore throat. It is likely that the subtle differences found in the OSA-COPD overlap syndrome might not cause relevant differences in short-term.

Nevertheless, when assessing the long-term consequences produced by the COPD condition, the subtle differences revealed here might be relevant, since they could be related to an increased risk of cardiovascular and cerebrovascular diseases. As a more severe OSA condition has been reported to increase these risks, it is likely that a persistent subtle worsening in the conditions might increase these risks as well, which would worsen the quality of life of COPD patients.

This situation would be even more relevant if we take into consideration that around 75-80% of OSA patients remain undiagnosed and untreated [11], which would be even more critical for the OSA-COPD patients, due to the increased risk to suffer cardiovascular or cerebrovascular diseases.

V. CONCLUSION

The consequences of an OSA-COPD overlap syndrome were explored from data of an epidemiological study. We analyzed a large sample of COPD patients who underwent PSG, which is usually a limiting factor when trying to assess the OSA-COPD overlap syndrome. Regarding the effects of COPD in sleep, our work revealed subtle differences when the COPD factor was compared versus non-COPD subjects. These subtle differences always revealed a worsening of the sleep parameters, which could be of importance when exposed for a prolonged period of time to these conditions. Finally, the OSA-COPD overlap syndrome should be considered as a prevalent and important condition to be treated, but, due to the difficulties of the COPD patients to perform sleep test, they usually remain OSA undiagnosed and untreated, which increases their risk to suffer from cardiovascular and cerebrovascular diseases.

ACKNOWLEDGMENT

The data used in this study have been provided by the Study of Health in Pomerania (SHIP) from the community Medicine Research Alliance of the Medical Faculty at the Ernst Moritz Arndt University of Greifswald (BMBF – Federal Ministry for Education and Research; Subsidy identification codes: 01ZZ9603, 01ZZ0103 and 01ZZ0701).

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