**A Comparison of nocturnal hypoxia markers in apnea patients with chronic obstructive pulmonary disease (COPD) and without it: A Cross-sectional study.**

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**Abstract:**

**Introduction:** Nocturnal hypoxemia has been shown to be associated with low quality of life and increased risk of mortality. The main causes are pulmonary diseases (like chronic obstructive pulmonary disorder- COPD) or Sleep related breathing disorders (like obstructive sleep apnea – OSA). In overlap syndrome, the co-existence of COPD and OSA, blood oxygen alteration and hypecapnia may be more severe.

We aimed to study hypoxemia markers in OSA, with and without COPD.

**Method:**  This cross sectional study evaluated clinical data and polysomnographic findings of 210 patients with AHIs > 5. Among them, 35 patients had COPD.

**Results:** 140 patients (66.7%) had severe OSA with AHIs ≥30. At wake stage, the mean oxygen saturation was 89.7 ± 5.1 mmHg for those with severe apnea, 91 ± 5.7 mmHg for non-severe apneas (AHI < 30),82.7 ± 10.1 mmHg for COPD patients with severe apneas, and 89.3 ± 7.5 mmHg for COPD with non-severe OSA (P value < 0.001). Mean PCO2 was 46.3 ± 7.1 mmHg for those with severe apnea, and 45 ± 7 mmHg for the others. It was 52.9 ± 7.6 mmHg for COPD patients with severe apneas, and 50.2 ± 10.1 mmHg with not-severe OSA (P value = 0.000).

The average percentage of sleep time spent with SpO2 fewer than 90% was 56.2 ± 40.2 in severe OSA group, 25.9 ± 36 in non-severe group, 75 ± 34.7 in COPD patients with severe apneas, and 42.3 ± 38.9 in COPD with non-severe apneas (P value = 0.000).

In average , blood oxygen saturation dropped to 68 ± 12.6 mmHg in severe OSA group, to 77 ± 11.6 mmHg in non-severe group, 57 ± 13.6 mmHg in COPD patients with severe OSA, and to 71 ± 17.8 mmHg in such patients with non-severe OSA (P value = 0.000).

**Conclusion:** Hypoxemia issignificantly prominent in overlap syndrome. The presence of diurnal hypoxemia and hypercapnia may predict nocturnal hypoxemia.

**Key words:** Nocturnal hypoxia, COPD, Sleep-disordered breathing, polysomnography

**Introduction**

Failure of ventilation because of pulmonary diseases may result in nocturnal hypoxemia and hypercapnia. Blood gas disturbances during sleep may also present in sleep disordered breathing without pulmonary disorders (1, 2).

Breathing stimulation during sleep is decreased compared with wake state. Ventilation and oxygenation during sleep rely mostly on chemical stimuli. As normal sleep reaches to deeper levels of sleep (N2 and N3), respiratory response to hypoxemia and hypercapnia decreased (3-5).Therefore, the threshold of blood PCo2 level which stimulates ventilation elevates from 40 mmHg in wake to 45 mmHg in sleep. Thus, alveolar ventilation decreases slightly and blood oxygen saturation drops for 3-4 percent (6) . In REM stage, because of muscle atonia (except for diaphragm) and irregular respiration, alveolar ventilation is even more disturbed. While normal individuals do not experience major alteration in PCO2 and PO2, at the presence of pulmonary diseases nocturnal blood gases change to some degrees.

Nocturnal hypoxemia is commonly seen with COPD. In a study, 27 to 70% of such patients suffered from nocturnal hypoxemia especially in REM stage, while diurnal study of PaO2 was normal (7).

**Definitions:**

**Nocturnal hypoxemia:** International classification of sleep disorders, the third revise (ICSD-3) define nocturnal oxygen desaturation (NOD) as PaO2 less than 88% in adults and 90% in children lasting for at least 5 minutes without hypoventilation (8).

**COPD:**  A type of [obstructive pulmonary disease](https://en.wikipedia.org/wiki/Obstructive_lung_disease) characterized by chronic abnormal airflow. 40% of these individuals suffer from sleep disturbances like difficulty in maintaining the continuity of sleep due to respiratory failure (9).More than half of these patients, whose diurnal SaO2 are above 90%, spend 30% of their sleep time with SaO2 less than 90% (10).

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**OSA:** A pathologic condition during sleep characterized by increased upper airway resistance and absence or decreased respiratory flow. By using polysomnographic findings, OSA is classified to mild (respiratory events represented by apnea-hypopnea index (AHI) more than 5) (11), moderate (AHI between 16 to 29) and severe (AHI ≥30) (12-16).

**Overlap syndrome**: This term was applied by Flenley for co-existence of OSA and COPD (17)\*. However, this term does not determine which condition is more severe and which treatment is more appropriate when one of two conditions is more prominent (18- 21). The important point is that this coincidence increases the risk of nocturnal oxygen desaturation and also diurnal hypoxemia and hypercapnia (22). Also, there are studies which have shown the increased risk of cardiovascular events and mortality rate due to overlap syndrome in comparison with each condition alone (23).

In summary, OSA may commonly be accompanied by pulmonary diseases, thus management strategies which cover both like non-invasive ventilation and oxygen therapy during night are pivotal. To best of our knowledge, there is no study on evaluation of nocturnal hypoxemia when COPD coexists with OSA. In this study we tried to determine hypoxemia markers and PaCO2 during sleep and wake in OSA patients with and without COPD, also their relation to major polysomnographic factors such as AHI.

**Materials and Method:**

In this cross sectional study, 307 adults (above 18 years of age) referred to Masih Daneshvari hospital for polysomnography during 2014-2015 entered. In order to normalize the data and enhance the accuracy of analysis, patients only underwent the test by Philips Respironic Alice 5 appliance were enrolled. Individuals without clear medical record, spirometery and gasometry (ABG) were excluded. All files were analyzed by software Sleepware G3 and related data including the lowest level of PaO2 during sleep, the percent of sleep time with SpO2 fewer than 90, AHI were achieved. To avoid the pulse oxymetery artifacts, SpO2s fewer than 50 considered as 50. Demographic parameters and spirometeric data and ABG were gathered from their medical records. Arterial SpO2 and partial pressure of carbon dioxide (PCO2) were recorded for each patient before the polysomnography test, when the patient was still awake. The average level of the lowest SpO2 was calculated.

 Then, the data was entered the software SPSS Statistic 23. The patients then divided to two groups according to AHI: severe sleep apnea (AHIs ≥30), and non-severe (AHI<30) group. COPD was diagnosed based on clinical records, spirometry test with FEV1/FVC less than 70%, and lung CT scan. At this stage, patients with cystic fibrosis, opium addiction and obesity hypoventilation syndrome (defined by BMI>30, diurnal PaCO2 > 45 mmHg and absence of other cardiopulmonary conditions) were deleted from the study. Ultimately Clinical and polysomnographic date of 210 patients were analyzed. In this manner, the above factors were evaluated and compared in the severe and non-severe sleep apnea, and in the COPD group (Overlap syndrome) and non-COPD group (OSA alone).

**Results**

97 (46.2%) males and 113 females (53.8%) aged from 54 to 89 years with mean age of 57 were enrolled. All of them had OSA (AHI>5). 25 patients (12%) suffered also from COPD, and the remained 185 ones did not have COPD. According to AHI, 140 patients (66.7%) labeled as severe OSA (with AHI≥30), while the others (33.3%) were in non-severe OSA group.

The mean SpO2 at the beginning of polysomnography (wake phase) for severe OSA group was 89.7 ± 5.1 mmHg, and 91 ± 5.7 mmHg for non-severe group. For COPD patients with severe apneas this figure was 82.7 ± 10.1 mmHg, and for COPD patients with non-severe apneas was 89.3 ± 7.5 mmHg (P value < 0.001).

The mean CO2 before the test was 46.3 ± 7.1 mmHg for those with severe apnea, and 45 ± 7 mmHg for the others. This figure was 52.9 ± 7.6 mmHg for COPD patients with severe apneas, and 50.2 ± 10.1 mmHg with not-severe OSA (P value = 0.000).

The average percentage of sleep time spent with SpO2 fewer than 90% was 56.2 ± 40.2 in severe OSA group, 25.9 ± 36 in non-severe group, 75 ± 34.7 in COPD patients with severe apneas, and 42.3 ± 38.9 in COPD patients with mild to moderate apneas (P Value = 0.000).

The average minimum SpO2 was 68 ± 12.6 mmHg in severe OSA group, and 77 ± 11.6 mmHg in non-severe group, 57 ± 13.6 mmHg in COPD patients with severe OSA, and to 71 ± 17.8 mmHg in such patients with mild to moderate OSA (P value = 0.000).

Table 1 demonstrates the above data.

**Discussion**

The mean SpO2 at wake phase is considerably low in coexisting of COPD and severe sleep apnea (82.7 ± 10.1 mmHg). Also, the average minimum SpO2 in COPD and severe OSA group was 16.2% lower than severe OSA group without COPD. Characteristically, the average percentage of sleep time spent with SpO2 less than 90% also increased with COPD superimposed on severe sleep apnea. Thus, wake hypoxemia and hypercapnia may predict nocturnal blood gas disturbances.

Pulmonary disease and some sleep-disordered breathing may result in more blood oxygen desaturation than normal sleep condition. Accordingly, and because of its consequences, in the last version of ICSD, nocturnal hypoxemia is defined as a separate sleep disorder (24-26).

Tidal volume is decreased slightly during normal sleep, even up to 15% in REM sleep (27)\* (34). Tidal volume in COPD sufferers decreased to 16% in NREM sleep and to 32% in REM sleep and this is another cause for nocturnal hypoxemia in such patients (28- 30). Lacasse Y et al found that 38% of their COPD patients who had mean diurnal SpO2 of 65 mmHg spent 30% of their night with SpO2 less than 90% (31). Thus, diurnal hypoxemia and PCO2 may predict somehow nocturnal hypoxemia (32, 33).

Flenley’ study showed that coexistence of OSA and COPD resulted in significant hypoxemia during sleep and similar to our study, it was correlated with AHI (17). Also in such patients, dyspnea and diurnal symptoms like tiredness is more prominent (34, 35).

Nocturnal hypoxemia due to pulmonary diseases usually last for several minutes or more, while when hypoxemia occurs following sleep apnea, it is shorter and recur frequently. The patients may be asymptomatic or suffer from sleep insufficiency, nocturnal dyspnea and excessive daytime sleepiness. Polycythemia is found frequently. Hypoxemia may result in serious consequences like pulmonary artery hypertension(36) , systemic hypertension (37,38), atherosclerosis and ischemic heart disease(39-41), cardiac arrhythmia (42), congestive heart failure(43), stroke (44) diabetes mellitus(45) and activated inflammatory mediators due to sleep fragmented(46-48).

Respiratory distress is enhanced during sleep in COPD patients. As PCo2 rises, their disease worsens. In this stage respiratory effort is more than patient’s ability. Consequently, decreased diaphragm force, edema and increased positive end pressure (PEEP) result in low tidal volume decompensated respiration. Appropriate non-invasive ventilation (NIV) can reduce muscle exhaustion and let compensated oxygenation restores that was monitoring during full PSG.

**Study limitation**

It seems that other variables such as mean apnea – hypopnea duration (AHD), and preferred apnea or hypopnea play important role in hypoxemia. Because of the software technical limitation, we were not able to determine AHD. Also the fragmented sleep due to respiratory disturbances did not allow the individual to enter REM sleep appropriately. Therefore, further investigation needs to determine the disturbances of blood oxygen in different stages of sleep.

The other one in the sleep lab was barometric pressure (655 mmHg), so Spo2 is lower than of sea level.

**Conclusion:**

The average percentage of sleep time spent with SpO2 fewer than 90 and the mean CO2 are increased significantly in COPD patients when complicated by severe OSA. Wake hypoxemia and hypercapnia may be a clue in making a diagnosis of pulmonary disease responsible for worsening the condition of OSA and can guide sleep clinics to draw a plan for appropriate treatment during sleep. In fact, nocturnal hypoxemia is necessary to be correct in order to improve diurnal hypoxemia and hypercapnia. To achieve this goal, cardiopulmonary reassessment is essential and the patients should be encouraged to have a plan for weight loss, opium and smoke cession. Besides, standard sleep study (polysomnography) is recommended; concurrently noninvasive ventilation and oxygen therapy should be applied.

**Conflict of interest:**

The authors declare that there was no conflict of interest in the current study foe them.

Table 1: **Comparison of the nocturnal hypoxia markers in OSA and Overlap syndrome**

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **AHI** | **COPD –** )mmHg( | **N** | **COPD +** )mmHg( | **N** |  Diff **% COPD±** | **P value** |
| **SPo2 َat** **base of the study** | <30 | 91.5(±5.7) | 33 | 89.3(±7.5) | 4 | 2.0% | 0.001 |
| 30≤ | 89.7(±5.1) | 43 | 82.7(±10.1) | 18 | 7.4% |
| **PCo2 at** **base of the study** | <30 | 45.0(±4.0) | 28 | 50.2(±7.1) | 3 | -11.6% | 0.000 |
| 30≤ | 46.3(±7.1) | 40 | 52.9(±7.6) | 21 | -14.3% |
| **Time spent with** **SpO2 less than 90%**  | <30 | 25.9%(±36.0) | 66 | 42.3%(±38.9) | 3 | 16.4% | 0.000 |
| 30≤ | 56.2%(±40.2) | 119 | 75.0%(±34.7) | 21 | 18.8% |
| **Minimum SpO2** **at average** | <30 | )11.6±(77.0 | 66 | ±(17.8)71.9 | 4 | 6.6% | 0.000 |
| 30≤ | ±(12.0)68.0 | 119 | ±(13,6)57.0 | 21 | 16.2% |

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