Predictive indexes of nocturnal desaturation in COPD patients not treated with long term oxygen therapy

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Abstract. – Nocturnal oxygen desaturation during the sleep is very frequent in patients affected by chronic obstructive pulmonary disease (COPD). Hypoventilation, rather than sleeping apnea, is commonly considered as the most relevant factor in the onset of nocturnal oxygen desaturation. On this topic, the Authors have carried on a study on the nocturnal hypoxemia in 70 hospitalized COPD patients with a mean FEV1% of 40 ± 21 and a mean PaO2 of 67.7 ± 6.1. Anthropometric features (sex, age, body mass index) and functional respiratory parameters (FEV1, FEV1/VC, PaO2, PaCO2, SaO2, pH) were considered. Moreover all the patients were monitored with transcutaneous pulse oxymetry, while breathing environmental air, in nighttime. Mean oxyhemoglobininc nocturnal saturation (SaO2 noct.%), minimum registered value of nocturnal SaO2 (min SaO2 noct.%), and the minutes of nighttime SaO2 < 90% and SaO2 < 85% (tSaO2 < 90% and tSaO2 < 85%) were considered. Fiftyfour patients (77.15%) were nocturnal desaturating (NOD), whereas 16 (22.85%) were not desaturating (nNOD). A statistically significant difference was found between the two groups as to the values of FEV1 (p < 0.05), PaCO2, pH, SaO2 noct.%, minimum SaO2 noct.% and tSaO2 < 90% and < 85% (p < 0.0001). A statistically significant correlation was found between tSaO2 < 90% and BMI (r = 0.44), PaCO2 (r = 0.48) and pH (r = -0.44), as well as between tSaO2 < 85% and PaCO2 (r = 0.57) and pH (r = -0.50), between SaO2 noct.% and BMI (r = -0.45), PaCO2 (r = -0.50), FEV1 (r = 0.44) and pH (r = 0.46) and finally between minimum SaO2 noct.% and PaCO2 (r = -0.47) was found.

Eighty percent of the NOD patients had PaO2 < 75 mm Hg and PaCO2 > 44 mm Hg. All the patients with PaCO2 > 50 mm Hg were NOD.

In conclusion, all COPD subjects with FEV1 < 49% and daytime PaO2 > 60 mm Hg, particularly when associated to elevated PaCO2 values and high BMI, should undergo a nocturnal pulse oxymetry in order to identify possible nocturnal desaturations. In these patients reduced FEV1, high BMI and/or elevated PaCO2 appear to be predictive indexes of nocturnal desaturation. A PaCO2 > 50 mm Hg is highly indicative for a nocturnal oxygen desaturation.

Key Words: Chronic obstructive pulmonary disease, Nocturnal hypoxaemia, Predictors, Nocturnal desaturation.

Introduction

Patients affected by Chronic Obstructive Pulmonary Disease (COPD), with PaO2 > 60 mm Hg when waking, who needn’t Long Term Oxygen Therapy (LTOT), can present episodes of hypoxemia during sleep1,2. These hypoxic events happen mainly in the REM (rapid eyes movements) sleep1,3-6. Such nocturnal hypoxic episodes are usually related to hypoventilation rather than to sleeping apnea3,6,7; many Authors, indeed, consider hypoventilation as the most relevant factor in the onset of oxyhemoglobininc desaturation during sleep, accompanied by retention of CO23,5,6,8-16.

Hypoxemia during sleep, in the opinion of Fletcher et al.1, can be found in about 27% of COPD patients. Vos et al instead, in a group of 60 patients, with a mean FEV1 of 43%, registered nighttime desaturations in 78% of the cases17. In a recent multicentric study on 94 COPD patients, with PaO2 ranging from 56 to 69 mm Hg and mean FEV1 of 1.0 L, Chaouat et al. underlined that 77% out of them presented nocturnal desaturation11.

It’s difficult to carry on a study on the sleep of all the COPD patients, so we tried...
to identify some data that could predict nocturnal hypoxemia in patients with daytime PaO₂ > 60 mm Hg, not treated with LTOT. The “blue and bloating” feature in COPD patients is a possible indicator of nocturnal hypoxemia. Furthermore, when daytime low PaO₂ and/or high PaCO₂ are present, nocturnal hypoxemia is registered: a statistically significant correlation, indeed, between daytime PaO₂ and/or SaO₂ and nighttime SaO₂ as well as between nighttime PaCO₂ and SaO₂, and nightly tSaO₂ < 90% is often reported. More over, a similar significant correlation between BMI (body mass index) and nighttime measured parameters, has been demonstrated. The hypercapnic and/or hypoxemic ventilatory response too, could predict the occurrence of nocturnal desaturation; the lower is the ventilatory response, the higher is the chance of nocturnal desaturation’s episodes. FEV₁ too, strongly correlates (r = 0.61) to transient lowering of nighttime SaO₂ (the lower is FEV₁, the more probably is to find out desaturating subjects); such correlation with SaO₂ has been demonstrated for the maximum inspiratory (r = 0.65) and trans-diaphragmatic (r = 0.53) muscular pressure, underlining that the muscular components are very important in determining nocturnal hypoxemia.

The aim of our study was to verify:

a) the incidence of nocturnal hypoxemia in a population of COPD affected subjects with PaO₂ > 60 mm Hg in waking;

b) to check out among the usually measured respiratory parameters, those that could predict an eventual nocturnal desaturation, so that we could choose the patients deserving to undergo controls by pulse oxymeter.

**Materials and Methods**

We checked nighttime pulse oxymetry in 70 hospitalized patients (54 males, 16 females), with a mean age of 65.03 years (± 9.7 SD), affected by COPD with FEV₁ < 65% and daytime PaO₂ ≥ 60 mm Hg, who need not LTOT according to the American Thoracic Society (ATS) guidelines. COPD was diagnosed according to criteria settled by the ATS. All the patients were in stable clinical conditions and underwent an optimized broncho-dilating treatment. We analyzed their anthropometric (sex, age, BMI) and functional respiratory features by spirometry (FEV₁, FEV₁/VC) and by arterial blood gas analysis, both while breathing environmental air and oxygen, (pH, PaO₂, PaCO₂, SaO₂). All the patients were monitored when sleeping by nighttime pulse oxymetry, while breathing environmental air. Mean oxyhemoglobin nocturnal saturation (SaO₂ noct.%), the minimum registered value of nocturnal SaO₂ (min SaO₂ noct.%) and the minutes of nighttime SaO₂ ≤ 90% and ≤ 85% (tSaO₂ ≤ 90 e ≤ 85%) were considered. We checked tSaO₂ ≤ 85% in order to evaluate the seriousness of the nocturnal hypoxemia. The respiratory functional tests were performed with Cosmed spirometer (Cosmed, Quark 4, Pavia-Rome, Italy). Arterial blood gas analysis was measured with the equipment ABL-500 (Radiometer Medical A/S, Copenhagen, Denmark). PaO₂ ≥ 75 mm Hg and PaCO₂ ≤ 44 mm Hg were considered as normal values.

We measured arterial blood oxygen saturation with the trans-cutaneous pulse oximeter equipment Pulsox-3 (Minolta, Osaka, Japan). Measurements were performed during the night time positioning the sensor on the second finger of the hand.

Patients who showed a pulse oxymetric plot with at least 5 minutes with SaO₂ ≤ 90% and a peak of SaO₂ ≤ 85%, were considered as nocturnal desaturating (NOD) according to the definition of Fletcher and coll. Obese patients, presenting a BMI more than 30 kg/m² for the males and 28.6 kg/m² for females, were left out of this study, as well as the snoring subjects, the ones who presented daytime sleeping and those with a neck measure > 39 cm, in order to exclude as far as possible subjects with an “overlap” syndrome.

For statistical analysis of the registered values we availed of the method of correlation and linear regression, as well as of the T-Student test for confronting the values in the different study population subsets; all the values were expressed as mean plus standard deviation (SD). P value was considered as positive only when < 0.05.
Results

In 70 hospitalized patients affected by COPD, with mean daytime PaO₂ 67.7 ± 6.1 mm Hg and mean FEV₁% 40 ± 21, nighttime pulse oxymetry was performed: 54 (77.15%) out of them were nightly desaturating patients (NOD), while 16 (22.85%) were not desaturating (nNOD) (see Table I).

A nophotometric, respiratory functional, arterial blood gas analysis and pulse oxymetry parameters are showed in Table I.

We found out a statistically significant difference between NOD and nNOD as for FEV₁ (p < 0.05), PaCO₂, pH, SaO₂ noct.%, minimum SaO₂ noct.%, tSaO₂ ≤ 90% and tSaO₂ ≤ 85% (p < 0.0001).

Among NOD subjects, 43 out of them (79.6%) presented PaO₂ < 75 mm Hg and PaCO₂ > 44 mm Hg; four (7.4%) had PaO₂ > 75 mm Hg and PaCO₂ > 44 mm Hg; four (7.4%) PaO₂ > 75 mm Hg and PaCO₂ < 44 mm Hg; three (6.6%) PaO₂ < 75 mm Hg and PaCO₂ < 44 mm Hg (see Figure 1).

All nNOD subjects, on the contrary, presented PaO₂ < 75 mm Hg and PaCO₂ < 47 mm Hg. A clu as, as showed in Figure 2, sorting out the patients of our study both NOD and nNOD by the different values of PaCO₂, we checked that all the patients with PaCO₂ < 35 mm Hg were not desaturating, whereas all the patients with PaCO₂ > 50 mm Hg were desaturating during the sleep.

In Table II various measured parameters are confronted with tSaO₂ noct. ≤ 90% and ≤ 85%, with SaO₂ noct.% and with minimum SaO₂ noct.%. A positive correlation between tSaO₂ ≤ 90% and BMI, and also with PaCO₂ (respectively p < 0.05 and p < 0.01, as well as a negative correlation with pH (p < 0.05) was evidenced. Such correlations resulted to be more significant for PaCO₂ (p < 0.0001) and pH (p = 0.0003) when confronted with tSaO₂ ≤ 85%. A negative correlation, furthermore, was noted both between SaO₂ noct.% with BMI (p < 0.01) and PaCO₂ (p < 0.001), whereas a positive correlation both with FEV₁ (p < 0.05) and pH (p < 0.01) was outlined. The minimum SaO₂ noct.% too, strongly correlates to PaCO₂ (p < 0.01)

Discussion

Our results show that in a high percentage of COPD subjects (77%) with daytime slight or medium oxygen desaturation (67.7 ± 6.1 mm Hg) and a mean FEV₁% 40 ± 21, the nighttime oxymetric plot presents more or less long periods of hypoxemia during sleep, according to many other Authors11,12,17. In our series all the subjects with FEV₁ > 1.45 L or > 49% of the theoretical value presented no nocturnal desaturation. In these patients, indeed, PaO₂ being equal, the FEV₁ resulted to

### Table I. Respiratory parameters measured in 70 COPD patients, divided in not nocturnal oxygen desaturating (nNOD) and desaturating (NOD). Anthropometric data, respiratory function, blood gas analysis and oxymetry were confronted for statistical analysis with Student T-test in both groups.

<table>
<thead>
<tr>
<th></th>
<th>All Mean ± SD</th>
<th>NOD Mean ± SD</th>
<th>nNOD Mean ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>54/16</td>
<td>10/6</td>
<td>44/10</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.2 ± 8.3</td>
<td>64.6 ± 5.8</td>
<td>65.73 ±10.1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 2.7</td>
<td>25.6 ± 1.7</td>
<td>26.9 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.2 ± 0.8</td>
<td>1.45 ± 0.88</td>
<td>1.02 ± 0.57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV₁/VC</td>
<td>43.2 ± 15.2</td>
<td>47.5 ± 13.7</td>
<td>40.6 ± 11.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV₁% pred.</td>
<td>40 ± 21</td>
<td>49 ± 18</td>
<td>37 ± 16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV₁/VC% pred.</td>
<td>53 ± 20</td>
<td>59 ± 18</td>
<td>51 ± 15</td>
<td></td>
</tr>
<tr>
<td>PaO₂ daytime (mm/Hg)</td>
<td>67.7 ± 6.1</td>
<td>66.8 ± 3.4</td>
<td>68.2 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>PaCO₂ daytime (mm/Hg)</td>
<td>49 ± 7.2</td>
<td>38.8 ± 3.9</td>
<td>50.4 ± 6.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>daytime arterial pH</td>
<td>7.4 ± 0.03</td>
<td>7.43 ± 0.03</td>
<td>7.39 ± 0.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SaO₂ daytime (%)</td>
<td>93.2 ± 2.3</td>
<td>93.3 ± 1.2</td>
<td>93.5 ± 2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SaO₂ noct. (%)</td>
<td>89 ± 3.4</td>
<td>92.2 ± 1.8</td>
<td>87.8 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>minimum SaO₂ noct. (%)</td>
<td>76.2 ± 15.1</td>
<td>83.6 ± 7.9</td>
<td>70.9 ± 9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>tSaO₂ noct. ≤ 90% (minutes)</td>
<td>105 ± 120.5</td>
<td>1.30 ± 1.7</td>
<td>128 ± 100.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>tSaO₂ noct. ≤ 85% (minutes)</td>
<td>23 ± 67.8</td>
<td>0.05 ± 0.1</td>
<td>37 ± 51.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
be significantly higher than in NOD subjects \((p < 0.05)\). This fact demonstrates that the more the respiratory function is impaired, the more likely these subjects will be nighttime hypoxemic. Fleetham et al., indeed, in a series of subjects with \(\text{FEV}_{1} < 26\%\), detected such condition in all cases\(^{19}\). These data match with those of De Marco et al. (mean \(\text{FEV}_{1} 0.9 \text{ L}\))\(^{18}\) and of Tatsumi et al. (\(\text{FEV}_{1}/\text{FVC} < 50\%\))\(^{20}\).

This is also confirmed by the significant correlation, outlined in our study, between \(\text{FEV}_{1}\) and mean \(\text{SaO}_{2}\) noct.\% (the worst \(\text{FEV}_{1}\) is, the lower mean \(\text{SaO}_{2}\) noct.\% is), according to other authors’ observations\(^{15}\). In fact, this statistical significance is very low in our study and gives no evidence when \(\text{FEV}_{1}\) is considered regard to the Vital Capacity (VC). This could be due to the broad variability of the \(\text{FEV}_{1}\) considered for the selection of our cases (\(\text{FEV}_{1} < 65\%\)), ranging from subjects with slight obstruction to those with severe obstruction. It is very likely that only for a certain value of bronchial obstruction nocturnal hypoxemia onsets. In our study only patients with \(\text{FEV}_{1} < 49\%\) resulted to desaturate. We noted, indeed, that hypoventilation, whose expression is the retention of \(\text{CO}_{2}\), is one of the major causes of nocturnal hypoxemia\(^{15,6,8,16}\) and it’s usually observed when \(\text{FEV}_{1}\) is less than 1 L or than 35\% of the predicted value\(^{8}\). \(\text{PaCO}_{2}\) resulted to be significantly higher in desaturating patients than in nNOD, as reported by other authors\(^{1,4,8,11-15}\), confirming that such subjects are “hypoventilating”. These patients are in an advanced stage of respiratory function impairment; they have severe obstruction and are “hyperinflated”, with an augmented respiratory dead space, so they tend to breath rapidly and superficially in order to reduce the inspiratory time, and therefore the work for respiration, and consequently to ease the muscle fatigue, specially the inspiratory one\(^{8}\). In these patients the diaphragm is chronically flattened, therefore in a disadvantageous position on its length/tension curve\(^{25}\); this fact determines a reduction
of the muscular inspiratory strength, and consequently a decrease of Current Volume and of ventilation, with further increase of arterial CO$_2$\textsuperscript{5,6,9,10,13}.

In our study we outlined that in COPD patients, with PaO$_2$ > 60 mm Hg, the daytime PaCO$_2$ is an important predictive index of nocturnal hypoxemia, according to the observations of many other authors\textsuperscript{1,4,8,11-15}. A statistically significant correlation, indeed, between this parameter and tSaO$_2$ $\leq$ 90% and mean SaO$_2$ noct.$\%$

**Predictive indexes for nocturnal hypoxaemia**

**Figure 2.** Percentage of patients Nocturnal Oxygen Desaturating (NOD) and not Desaturating (nNOD) on the basis of PaCO$_2$ values.

![Figure 2](image)

**Table II.** Observed correlation (r) between mean time of night O$_2$ saturation $\leq$ 90% (tSaO$_2$ noct $\leq$ 90), or $\leq$ 85% (tSaO$_2$ noct $\leq$ 85), mean night O$_2$ saturation (mean noct SaO$_2$ $\%$), minimum night O$_2$ saturation value (min. SaO$_2$ $\%$) and the various considered parameters in NOD subjects.

<table>
<thead>
<tr>
<th></th>
<th>tSaO$_2$ noct $\leq$ 90%</th>
<th>tSaO$_2$ noct $\leq$ 85%</th>
<th>mean noct SaO$_2$ $%$</th>
<th>min. noct SaO$_2$ $%$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>BMI</td>
<td>0.442</td>
<td>&lt; 0.05</td>
<td>-0.452</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>0.444</td>
<td>&lt; 0.05</td>
<td>-0.501</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV$_1$/VC</td>
<td>0.422</td>
<td>&lt; 0.05</td>
<td>-0.501</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV$_1$/VC%</td>
<td>0.444</td>
<td>&lt; 0.05</td>
<td>-0.501</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daytime PaO$_2$</td>
<td>0.484</td>
<td>&lt; 0.01</td>
<td>0.577</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Daytime arterial pH</td>
<td>-0.439</td>
<td>&lt; 0.05</td>
<td>-0.501</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daytime SaO$_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only significant correlations (p) are reported. 
(\(p < 0.05\))
was detected: the higher hypercapnia is, the lower the SaO₂ noct.% is, whereas the higher tSaO₂ ≤ 90% is. This demonstrates that hypoventilation is without any doubt one of the most important causes of nocturnal hypoxemia in COPD patients. Moreover, a very strong correlation between PaCO₂ and tSaO₂ ≤ 90%, and the minimum value of SaO₂ noct.% was evidenced: the higher PaCO₂ is (that is the more hypoventilation), the more serious nocturnal hypoxemia is. Hypoventilation is determined by the muscular power; in COPD patients, as we already said, this is very reduced 5,6,9,10,13, and in fact these patients show a significant correlation between maximum inspiratory mouth pressure (PImax) and the mean SaO₂ noct.% 13. We can infer from our data that all the subjects with PaCO₂ > 50 mm Hg are nocturnal desaturating. Such value (PaCO₂ > 50 mm Hg), represents the threshold across which, in COPD subjects with slight or mild hypoxemia, the risk of nocturnal desaturation highly increases.

The BMI is another predictive parameter of nocturnal hypoxemia 11. In this study we observed a significant correlation between BMI and the mean tSaO₂ ≤ 90%, and the mean SaO₂ noct.; as the weight increase, a worsening of the nocturnal hypoxemia is registered. Obesity associated to COPD, indeed, can be extremely unfavourable in respect of the respiratory function, determining a further worsening of hypoventilation and the occurrence of longer periods of nocturnal hypoxemia 8.

In our case-load, disaccording to other observations 2,10,12, PaO₂ doesn’t seem to be a predictive index of nocturnal desaturations, since no statistically significant correlations with nighttime SaO₂ were observed.

Most of the NOD subjects (79.6%) presented a PaO₂ < 75 mm Hg and PaCO₂ > 44 mm Hg, as to confirm the importance of values of PaCO₂ as a predictive index of nocturnal hypoxemia. Nevertheless, we must outline that in 12.9% of the NOD patients (7/54 pts) PaCO₂ resulted to be less than 44 mm Hg, with PaO₂ < 75 mm Hg in 6.6% (3 pts) and PaO₂ > 75 mm Hg in 7.4% (4 pts). In these subjects with normal daytime PaCO₂, it’s very likely that the mechanism determining nocturnal hypoxemia is not hypoventilation, but the alteration of ventilation/perfusion ratio 5,9,10. In fact, in these patients with inadequate mucous-ciliary clearance, the absence of cough reflex drive during sleep could determine a worsening of the ventilation/perfusion ratio, due to the piling up of the mucus in lower respiratory tract.

In 14.8% (8 pts) of the NOD patients, on the contrary, a normal daytime PaO₂ (> 75 mm Hg) was registered; this disagree with other authors 11,12, who assert that patients with normal daytime PaO₂ don’t develop nocturnal hypoxemia. It is likely that these subjects during daytime, in orthostatic position can keep up an adequate oxygenation of the blood, that becomes inadequate during the night in clinostatic position.

In 7.4% (4 pts) of the NOD patients arterial blood gas analysis was quite normal; these patients could escape a pulse oxymetric study.

In conclusion, all the COPD subjects with FEV₁ < 49% who presented daytime PaO₂ > 60 mm Hg in resting conditions, particularly when elevated PaCO₂ values and high BMI are associated, should undergo a nocturnal pulse oxymetry in order to identify possible nocturnal desaturations. In these patients a reduced FEV₁, a high BMI and/or an elevated PaCO₂ appear to be predictive indexes of nocturnal desaturation. In COPD subjects with slight or mild hypoxemia, PaCO₂ > 50 mm Hg is highly predictive for a nocturnal desaturation. Notwithstanding, even if in a minor percentage, subjects with normal daytime PaO₂ and PaCO₂ could show in the pulseoxymetric plot episodes of nocturnal hypoxemia during sleep.

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