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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 FEV_1% of 40 ± 21 and a mean PaO_2 of 67.7 ± 6.1. Anthropometric features (sex, age, body mass index) and functional respiratory parameters (FEV_1, FEV_1/VC, PaO_2, $PaCO_2$, SaO_2, pH) were considered. Moreover all the patients were monitorized with transcutaneous pulse oxymetry, while breathing environmental air, in nighttime. Mean oxyhemoglobinic nocturnal saturation (SaO_2 noct.%), minimum registered value of nocturnal SaO_2 (min SaO_2 noct.%) and the minutes of nighttime $SaO_2 \leq 90\%$ and $\leq 85\%$ ($tSaO_2 \leq 90\%$ e $\leq 85\%$) 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 FEV_1 ($p < 0.05$), $PaCO_2$, pH, SaO_2 noct.%, minimum SaO_2 noct.% and $tSaO_2 \leq 90\%$ and $\leq 85\%$ ($p < 0.0001$). A statistically significant correlation was found between $tSaO_2 < 90\%$ and BMI (r = 0.44), $PaCO_2$ (r = 0.48) and pH (r = -0.44), as well as between $tSaO_2 < 85\%$ and $PaCO_2$ (r = 0.57) and pH (r= -0.50), between SaO_2 noct.% and BMI (r = -0.45), $PaCO_2$ (r = -0,50), FEV_1 (r = 0.44) and pH (r = 0.46) and finally between minimum SaO_2 noct.% and $PaCO_2$ (r = -0.47) was found.**

Eighty percent of the NOD patients had $PaO_2 < 75$ mm Hg and $PaCO_2 > 44$ mm Hg. All the patients with $PaCO_2 > 50$ mm Hg were NOD.

In conclusion, all COPD subjects with $FEV_1 < 49\%$ and daytime $PaO_2 > 60$ mm Hg, particularly when associated to elevated $PaCO_2$ values and high BMI, should undergo a nocturnal pulse oxymetry in order to identify possible nocturnal desaturations. In these patients reduced FEV_1, high BMI and/or elevated $PaCO_2$ appear to be predictive indexes of nocturnal desaturation. A $PaCO_2 > 50$ 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 $PaO_2 > 60$ mm Hg when waking, who needn't Long Term Oxygen Therapy (LTOT), can present episodes of hypoxemia during sleep[1,2]. These hypoxemic events happen mainly in the REM (rapid eyes movements) sleep[1,3-6]. Such nocturnal hypoxemic episodes are usually related to hypoventilation rather than to sleeping apnea[3,6,7]; many Authors, indeed, consider hypoventilation as the most relevant factor in the onset of oxyhemoglobinic desaturation during sleep, accompained by ritention of CO_2[3,5,6,8-16].

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 FEV_1 of 43%, registered nighttime desaturations in 78% of the cases[17]. In a recent multicentric study on 94 COPD patients, with PaO_2 ranging from 56 to 69 mm Hg and mean FEV_1 of 1.0 L, Chaouat et al. underlined that 77% out of them presented nocturnal desaturation[11].

It's difficult to carry on a study on the sleeep of all the COPD patients, so we tried

to identify some data that could predict nocturnal hypoxemia in patients with daytime PaO_2 > 60 mm Hg, not treated with LTOT. The "blue and bloating" feature in COPD patients is a possible indicator of nocturnal hypoxemia[9,18]. Furthermore, when daytime low PaO_2 and/or high $PaCO_2$ are present, nocturnal hypoxemia is registered: a statistically significant correlation, indeed, between daytime PaO_2 and/or SaO_2 and nighttime SaO_2[2,4,10,12-15] as well as between nighttime $PaCO_2$ and SaO_2, and nightly $tSaO_2$ < 90% is often reported[1,4,8,11,13-15]. More over, a similar significant correlation between BMI (body mass index) and nighttime measured parameters, has been demonstrated[11]. 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[12,19,20]. FEV_1 too, strongly correlates (r = 0.61) to transient lowering of nighttime SaO_2 (the lower is FEV_1, the more probably is to find out desaturating subjects)[13]; such correlation with SaO_2 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[13,16].

The aim of our study was to verify:

a) the incidence of nocturnal hypoxemia in a population of COPD affected subjects with PaO_2 > 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 FEV_1 < 65% and daytime PaO_2 ≥ 60 mm Hg, who need not LTOT according to the American Thoracic Society (ATS) guidelines[21,22]. COPD was diagnosed according to criteria settled by the ATS[21,22]. 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 (FEV_1, FEV_1/VC) and by arterial blood gas analysis, both while breathing environmental air and oxygen, (pH, PaO_2, $PaCO_2$, SaO_2). All the patients were monitored when sleeping by nighttime pulse oxymetry, while breathing environmental air. Mean oxyhemoglobinic nocturnal saturation (SaO_2 noct.%), the minimum registered value of nocturnal SaO_2 (min SaO_2 noct.%) and the minutes of nighttime SaO_2 ≤ 90% and ≤ 85% ($tSaO_2$ ≤ 90 e ≤ 85%) were considered. We checked $tSaO_2$ ≤ 85% in order to evaluate the seriousness of the nocturnal hypoxemia. The respiratory functional tests were performed with Cosmed spirometer (Cosmed, Quark 4, Pavona-Rome, Italy). Arterial blood gas analysis was measured with the equipement ABL-500 (Radiometer Medical A/S, Copenhagen, Denmark). PaO_2 ≥ 75 mm Hg and $PaCO_2$ ≤ 44 mm Hg were considered as normal values.

We measured arterial blood oxygen saturation with the trans-cutaneous pulse oxymeter equipement 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 SaO_2 ≤ 90% and a peak of SaO_2 ≤ 85%, were considered as nocturnal desaturating (NOD) according to the definition of Fletcher and coll[23].

Obese patients, presenting a BMI more than 30 kg/m^2 for the males and 28.6 kg/m^2 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[24].

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 PaO_2 67.7 ± 6.1 mm Hg and mean FEV_1% 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).

Anthropometric, 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 FEV_1 ($p < 0.05$), $PaCO_2$, pH, SaO_2 noct.%, minimum SaO_2 noct.%, $tSaO_2 \leq 90\%$ and $tSaO_2 \leq 85\%$ ($p < 0.0001$).

Among NOD subjects, 43 out of them (79.6%) presented $PaO_2 < 75$ mm Hg and $PaCO_2 > 44$ mm Hg; four (7.4%) had $PaO_2 > 75$ mm Hg and $PaCO_2 > 44$ mm Hg; four (7.4%) $PaO_2 > 75$ mm Hg and $PaCO_2 < 44$ mm Hg; three (6.6%) $PaO_2 < 75$ mm Hg and $PaCO_2 < 44$ mm Hg (see Figure 1).

All nNOD subjects, on the countrary, presented $PaO_2 < 75$ mm Hg and $PaCO_2 < 47$ mm Hg. Actually, as showed in Figure 2, sorting out the patients of our study both NOD and nNOD by the different values of $PaCO_2$, we checked that all the patients with $PaCO_2 <$ 35 mm Hg were not desaturating, whereas all the patients with $PaCO_2 > 50$ mm Hg were desaturating during the sleep.

In Table II various measured parameters are confronted with $tSaO_2$ noct. ≤ 90% and ≤ 85%, with SaO_2 noct.% and with minimum SaO_2 noct.%. A positive correlation between $tSaO_2 \leq 90\%$ and BMI, and also with $PaCO_2$ (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 $PaCO_2$ ($p < 0.0001$) and pH ($p = 0.0003$) when confronted with $tSaO_2 \leq 85\%$. A negative correlation, furthermore, was noted both between SaO_2 noct.% with BMI ($p < 0.01$) and $PaCO_2$ ($p < 0.001$), whereas a positive correlation both with FEV_1 ($p < 0.05$) and pH ($p < 0.01$) was outlined. The minimum SaO_2 noct.% too, strongly correlates to $PaCO_2$ ($p < 0.01$)

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 FEV_1% 40 ± 21, the nighttime oxymetric plot presents more or less long periods of hypoxemia during sleep, according to many other Authors[11,12,17]. In our series all the subjects with $FEV_1 > 1.45$ L or > 49% of the theoretical value presented no nocturnal desaturation. In these patients, indeed, PaO_2 being equal, the FEV_1 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.

	All *Mean ± SD*	*nNOD* *Mean ± SD*	*NOD* *Mean ± SD*	*p*
Sex (M/F)	54/16	10/6	44/10	
Age (yr)	65.2 ± 8.3	64.6 ± 5.8	65.73 ±10.1	
BMI (kg/m^2)	26.1 ± 2.7	25.6 ±1.7	26.9 ± 2.3	
FEV_1 (L)	1.2 ± 0.8	1.45 ± 0.88	1.02 ± 0.57	< 0.05
FEV_1/VC	43.2 ± 15.2	47.5 ± 13.7	40.6 ± 11.7	
FEV_1% pred.	40 ± 21	49 ± 18	37 ± 16	< 0.05
FEV_1/VC% pred.	53 ± 20	59 ± 18	51 ± 15	
PaO_2 daytime (mm/Hg)	67.7 ± 6.1	66.8 ± 3.4	68.2 ± 5.2	
$PaCO_2$ daytime (mm/Hg)	49 ± 7.2	38.8 ± 3.9	50.4 ± 6.9	< 0.0001
daytime arterial pH	7.4 ± 0.03	7.43 ± 0.03	7.39 ± 0.03	< 0.0001
SaO_2 daytime (%)	93.2 ± 2.3	93.3± 1.2	93.5 ± 2.1	
SaO_2 noct. (%)	89 ± 3.4	92.2 ± 1.8	87.8 ± 2.1	< 0.0001
minimum SaO_2 noct. (%)	76.2 ± 15.1	83.6 ± 7.9	70.9 ± 9.1	< 0.0001
$tSaO_2$ noct. ≤ 90% (minutes)	105 ± 120.5	1.30 ± 1.7	128 ± 100.3	< 0.0001
$tSaO_2$ noct. ≤ 85% (minutes)	23 ± 67.8	0.05 ± 0.1	37 ± 51.2	< 0.0001

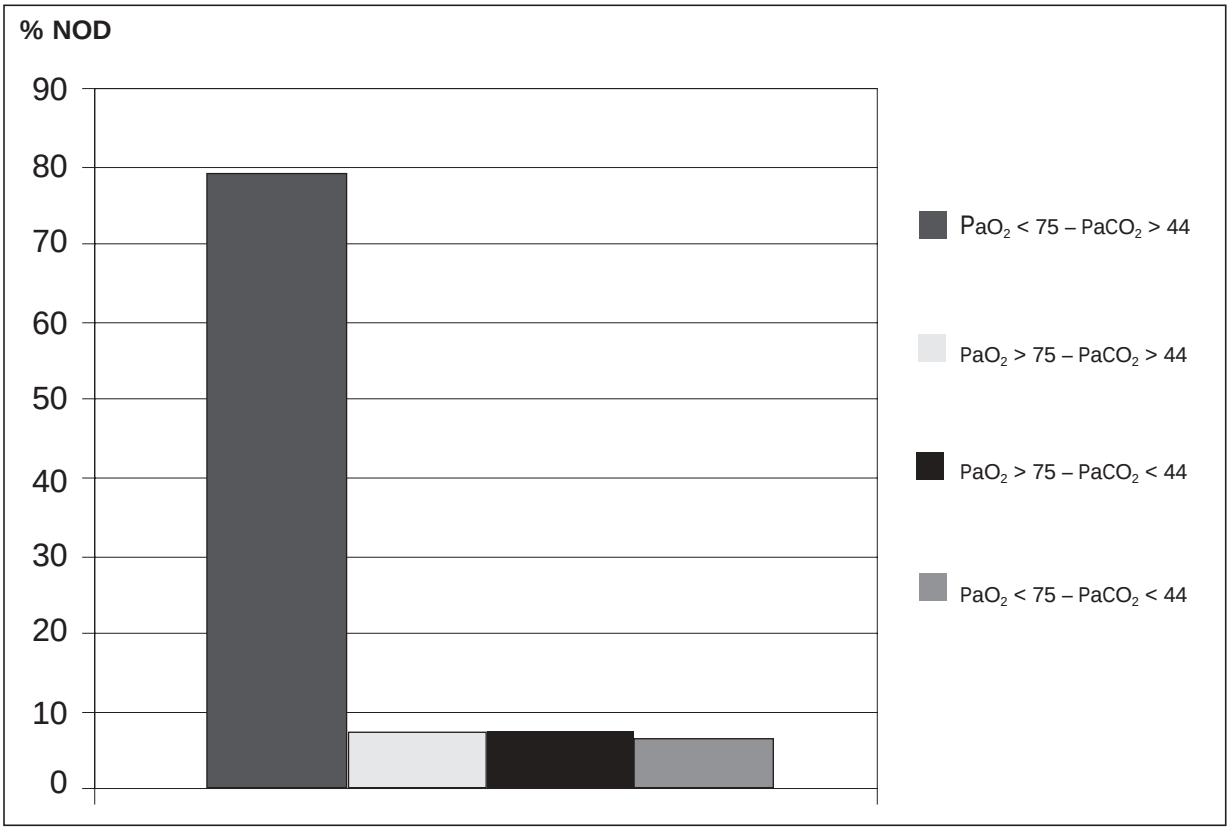

Figure 1. Nocturnal Oxygen Desaturating (NOD) patients from our study, divided in groups on the basis of the arterial blood gas analysis data.

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 $FEV_1 < 26\%$, detected such condition in all cases[19]. These data match with those of De Marco et al. (mean FEV_1 0.9 L)[18] and of Tatsumi et al. ($FEV_1/FVC < 50\%$)[20]. This is also confirmed by the significant correlation, outlined in our study, between FEV_1 and mean SaO_2 noct.% (the worst FEV_1 is, the lower mean SaO_2 noct.% is), according to other Authors' observations[13]. In fact, this statistical significancy is very low in our study and gives no evidence when FEV_1 is considered regard to the Vital Capacity (VC). This could be due to the broad variability of the FEV_1 considered for the selection of our cases ($FEV_1 < 65\%$), 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 $FEV_1 < 49\%$ resulted to desaturate. We noted, indeed, that hypoventilation, whose expression is the ritention of CO_2, is one of the major causes of nocturnal hypoxemia[3,5,6,8-16] and it's usually observed when FEV_1 is less than 1 L or than 35% of the predicted value[8]. $PaCO_2$ 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[4,8]. In these patients the diaphragm is chronically flattened, therefore in a disadvantageous position on its length/tension curve[25]; this fact determines a reduction

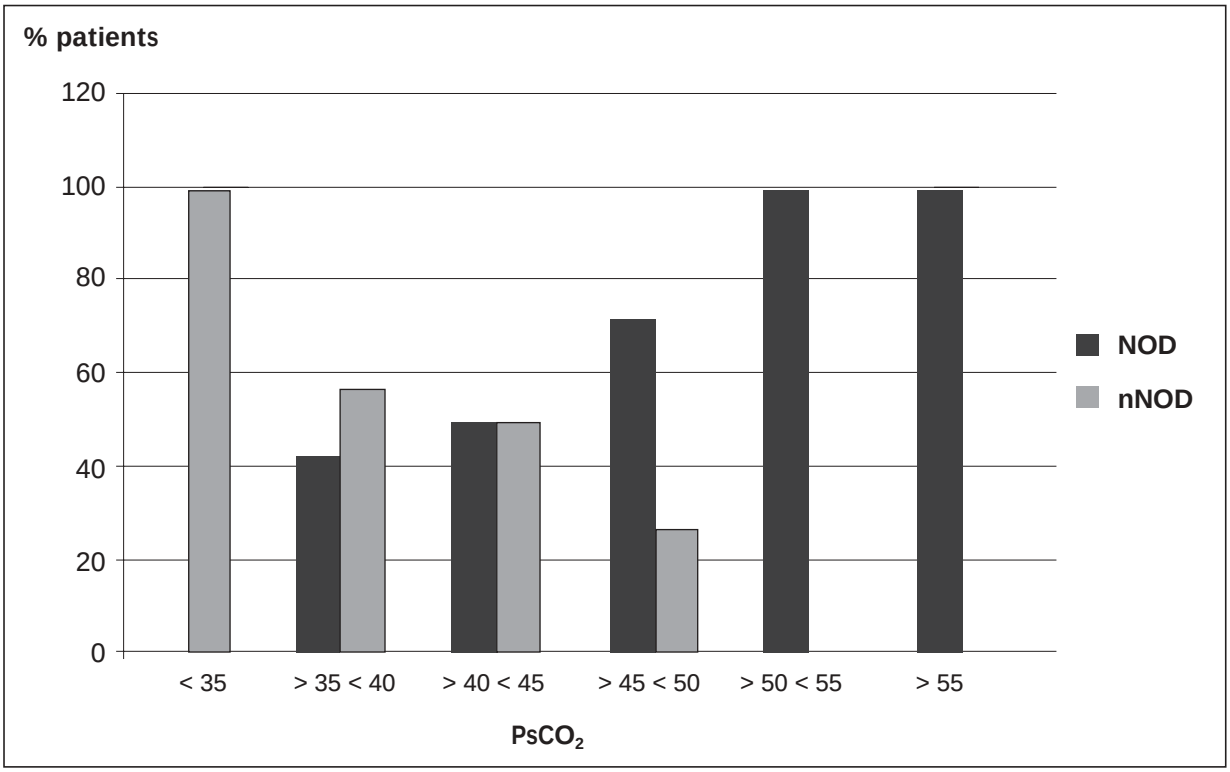

Figure 2. Percentage of patients Nocturnal Oxygen. Desaturating (NOD) and not Desaturating (nNOD) on the basis of $PaCO_2$ values.

of the muscular inspiratory strenght, and consequently a decrease of Current Volume and of ventilation, with further increase of arterial CO_2[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[1,4,8,11-15]. A statistically significant correlation, indeed, between this parameter and $tSaO_2 \leq 90\%$ and mean SaO_2 noct.%

Table II. Observed correlation (r) between mean time of night O_2 saturation ≤ 90% ($tSaO_2$ noct ≤ 90), or ≤ 85% ($tSaO_2$ noct ≤ 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.

	$tSaO_2$ noct ≤ 90%		***$tSaO_2$ noct ≤ 85%***		***mean noct SaO_2%***		***min. noct SaO_2%***	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***
BMI	0.442	< 0.05			-0.452	< 0.01		
FEV_1 (L)					0.444	< 0.05		
FEV_1%					0.422	< 0.05		
FEV_1/VC								
FEV_1/VC%								
Daytime PaO_2								
Daytime $PaCO_2$	0.484	< 0.01	0.577	< 0.0001	-0.505	< 0.001	-0.467	< 0.01
Daytime arterial pH	-0.439	< 0.05	-0.501	< 0.001	0.464	< 0.01		
Daytime SaO_2								

Only significant correlations (p) are reported.
($p < 0.05$)

was detected: the higher hypercapnia is, the lower the SaO_2 noct.% is, whereas the higher $tSaO_2 \leq 90\%$ is. This demonstrates that hypoventilation is without any doubt one of the most important causes of nocturnal hypoxemia in COPD patients. More over, a very strong correlation between $PaCO_2$ and $tSaO_2 \leq 85\%$, and the minimum value of Sa O_2 noct.% was evidenced: the higher $PaCO_2$ 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 (PI_{max}) and the mean SaO_2 noct.%[13]. We can infer from our data that all the subjects with $PaCO_2 > 50$ mm Hg are nocturnal desaturating. Such value ($PaCO_2 > 50$ 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 $tSaO_2 \leq 90\%$, and the mean SaO_2 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], PaO_2 doesn't seem to be a predictive index of nocturnal desaturations, since no statistically significant correlations with nighttime SaO_2 were observed.

Most of the NOD subjects (79.6%) presented a $PaO_2 < 75$ mm Hg and $PaCO_2 > 44$ mm Hg, as to confirm the importance of values of $PaCO_2$ as a predictive index of nocturnal hypoxemia. Nevertheless, we must outline that in 12.9% of the NOD patients (7/54 pts) $PaCO_2$ resulted to be less than 44 mm Hg, with $PaO_2 < 75$ mm Hg in 6.6% (3 pts) and $PaO_2 > 75$ mm Hg in 7.4% (4 pts). In these subjects with normal daytime $PaCO_2$, 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 countrary, a normal daytime PaO_2 (> 75 mm Hg) was registered; this disagree with other authors[11,12], who assert that patients with normal daytime PaO_2 don't develope 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 $FEV_1 < 49\%$ who presented daytime $PaO_2 > 60$ mm Hg in resting conditions, particularly when elevated $PaCO_2$ values and high BMI are associated, should undergo a nocturnal pulse oxymetry in order to identify possible nocturnal desaturations. In these patients a reduced FEV_1, a high BMI and/or an elevated $PaCO_2$ appear to be predictive indexes of nocturnal desaturation. In COPD subjects with slight or mild hypoxemia, $PaCO_2 > 50$ mm Hg is highly predictive for a nocturnal desaturation. Notwithstanding, even if in a minor percentage, subjects with normal daytime PaO_2 and $PaCO_2$ could show in the pulsoxymetric plot episodes of nocturnal hypoxemia during sleep.

References

1) *Fletcher EC, Miller J, Divine GW, Fletcher JC, Miller T.* Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxigen tensions above 60 mm Hg. Chest 92: 604-608, 1987.

2) *Levi-Valensi P, Weitzenblum E, Rida Z, Anbri P, Braghiroli A, Donner C, Aprill M, Zielinski J, Wurtemberger G.* Sleep-related oxygen desaturation and daytime pulmonary hemodynamics in COPD patients. Eur Respir J 1992; 5: 301-307.

3) *Hudgel DW, Martin RJ, Capehart M, Johnson B, Hill P.* Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. J Appl Physiol 1983; 55: 669-677.

4) *Douglas NJ*. Sleep in patients with chronic obstructive pulmonary disease. Clin Chest Med 1998; 19: 115-125.

5) *Fletcher EC, Gray BA, Levin DC*. Non-apneic mechanism of arterial oxygen desaturation during rapid eye movement sleep. J Appl Physiol 1983; 54: 632-639.

6) *Becker HF, Piper AJ, Flinn WE, McNamara SG, Grunstein RR, Peter JH, Sullivan CE*. Breathing during sleep in patients with nocturnal desaturation. Am J Respir Crit Care Med 1999; 159: 112-118.

7) *Catterall JR, Douglas NJ, Calverley PMA, Shapiro CM, Douglas NJ, Flenley DC*. Transient hypoxemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. Am Rev Respir Dis 1983; 128: 24-29.

8) *Krachman S, Criner GJ*. Hypoventilation syndromes. Clin Chest Med 1998; 19: 139-155.

9) *Catterall JR, Calverley PMA, Macnee W, Warren PM, Shapiro CM, Douglas NJ, Flenley DC*. Mechanisms of transient nocturnal hypoxaemia in hypoxic chronic bronchitis and emphysema. J Appl Physiol 1985; 159: 1689-1703.

10) *Mulloy E, McNicholas WT*. Ventilation and gas exchange during sleep and exercise in severe COPD. Chest 1996; 109: 387-394.

11) *Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, et al.* Sleep related SaO_2 desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. Eur Respir J 1997; 10: 1730-1735.

12) *Vos PJE, Folgering H, van Herwaarden CLA*. Predictors for nocturnal hypoxaemia (mean SaO_2 < 90%) in normoxic and middly hypoxic patients with COPD. Eur Respir J 1995; 8: 74-77.

13) *Heijdra YF, Dekhuijzen PNR, van Herwaarden CLA, Folgering HTM.* Nocturnal saturation and respiratory muscle function in patients with chronic obstructive pulmonary disease. Thorax 1995; 50: 610-612.

14) *Bradley TD, Mateika J, Li D, Avendano M, Goldstein RS*. Daytime hypercapnia in the development of nocturnal hypoxaemia in COPD. Chest 1990; 97: 308-312.

15) *McKeon JL, Murree-Allan K, Saunders NA*. Prediction of oxygenation during sleep in patients with chronic obstructive lung disease. Thorax 1988; 43: 312-317.

16) *Heijdra YF, Dekhuijzen PNR, van Herwaarden CLA, Folgering HTM.* The relationship between nocturnal oxygen desaturations and inspiratory muscle strength in COPD. Eur Respir J 1992; 5 (Suppl. 15): 25S-26S.

17) *Vos PJE, Folgering H, van Herwaarden CLA*. Prevalence of oxygen desaturations and associated breathing disorders during sleep in patients with chronic obstructive pulmonary disease. In Sleep and health risk. Peter J, Penzel T, Todzus T, Wichert PV eds Springer Verlag, Berlin 1991; pp 246-250.

18) *De Marco FJ, Wynne JW, Block AJ, Boysen PG, Tassan VC*. Oxygen desaturation during sleep as a determinant of the "blue and bloated" syndrome. Chest 1981; 79: 621-625.

19) *Fleetham JA, Mezon B, West P, Bradley CA, Anthonisen NR, Kryger MH.* Chemical control of ventilation and sleep desaturation in patients with COPD. Am Rev Respir Dis 1980; 122: 583-589.

20) *Tatsumi K, Kimura H, Kunitomo F, Kuriyama T, Watanabe S, Honda Y.* Sleep arterial oxygen desaturation and chemical control of breathing during wakefulness in COPD. Chest 1986; 90: 68-73.

21) *Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995; 8: 1398-1420.

22) *ATS*. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152; S72-S120.

23) *Fletcher EC, Scott D, Qian W, Luckett RA, Miller CC, Goodnight-White S*. Evolution of nocturnal oxyhemoglobin desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO_2 above 60 torr. Am Rev Respir Dis 1991; 144: 401-425.

24) *Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R*. Association of chronic obstructive pulmonary disease and sleep apnoea syndrome. Am J Respir Crit Care Med 1995; 151; 82-86.

25) *Rochester DF, Braun NMT*. Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis 1985; 132: 42-72.