PREDICTORS OF NOCTURNAL DESATURATION IN PATIENTS WITH STABLE COPD

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ПРОГНОСТИЧЕСКИЕ ФАКТОРЫ НОЧНОЙ ДЕСАТУРАЦИИ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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Summary. Detection of nocturnal hypoxemia, in normoxic or mildly hypoxic COPD patients seems clinically relevant, since this feature can cause serious problems like pulmonary hypertension and cardiac arrhythmia. In current study, we aimed to identify factors, which might predict nocturnal desaturation (ND).We studied 38 COPD patients with a mean age of 62, 7± 7, 9 and mean FEV_1 of 45, 6±12,3. Day time blood gas values, spirometry, CO diffusing capacity, maximum inspiratory and expiratory mouth pressures, 6-minute walk test, BMI, skin fold thickness, handgrip force, nocturnal oxygen saturation(SaO_2) were measured. ND was considered when there was a fall in SaO_2 below 90% for 5 minutes and more. 16 patients experienced ND. Desaturators had a significantly lower daytime PaO_2 (p=0,004), SaO_2 (p=0,001) and FEV_1 %(p=0, 05) than non-desaturators. 6-minute walk test correlated with ND (sensitivity 62%, specificity 76%, and positive predictive value 66%). We also found positive correlation between mean nocturnal SaO_2 and daytime PaO2, SaO_2, FEV_1 %, DLCO %. Stepwise regression analysis revealed that daytime SaO_2 was the only independent predictor of mean nocturnal SaO_2. We observed no ND in patients with daytime $SaO_2 \geq 95\%$ and $PaO_2 \geq 80$mmHg.We concluded that daytime SaO_2 is helpful in predicting nocturnal hypoxemia.

Key words: nocturnal desaturation, desaturator, chronic obstructive pulmonary disease

Резюме. Выявление у больных хронической обструктивной болезнью легких (ХОБЛ) выраженной гипоксемии, недостаточно выраженной гипоксемии или нормального содержания кислорода в крови в ночное время суток представляет клиническую значимость, так как эта функция может привести к серьезным проблемам, таким как легочная гипертензия и сердечная аритмия.
В данной работе мы постарались определить факторы, которые могли бы предсказать появление ночной десатурации (НД). Мы изучили данные, полученные в результате исследования 38 пациентов с ХОБЛ, с показателями 7+ 7,9 и $ОФВ_1$ 45,6 +12,3, средний возраст которых составил 62 года. Производились дневные замеры насыщенности крови газом, спирометрии, диффузиозной ёмкости (CO), давления в ротовой полости во время вдоха и выдоха, 6-минутной ходьбы, индекса массы тела, толщины кожной складки, силы сжатия руки, ночного насыщения кислородом (SaO_2). Ночная десатурация наблюдалась тогда, когда показатели SaO_2 были ниже 90% на протяжении 5 минут и более. НД проявилась у 16 пациентов. Десадураторы имели значительно более низкие дневные показатели PaO_2 (p=0,004), SaO_2 (p=0,001) и $ОФВ_1$ %(p=0, 05), чем не десадураторы. Тест 6-минутной ходьбы коррелирует с НД (чувствительность 62%, специфичность 76% и положительная прогностическая ценность 66%). Мы также обнаружили положительную корреляцию между средними ночными показателями SaO_2 и дневными показателями PaO_2, SaO_2, ОФВ1%, DLCO%. Поэтапный регрессионный анализ показал, что дневной показатель SaO_2 являлся единственным независимым прогностическим фактором среднего ночного показателя SaO_2. Мы не наблюдали НД у пациентов с дневными показателями $SaO_2 \geq 95\%$ и $PaO2 \geq 80$mmHg. мы пришли к выводу, что дневной показатель SaO_2 может являться прогностическим фактором ночной гипоксемии.

Ключевые слова: ночная десатурация, десатуратор, хроническая обструктивная болезнь легких

Patients with chronic obstructive pulmonary disease (COPD) have varying degrees of arterial oxygen desaturation during sleep. Nocturnal desaturation is greater during sleep than during maximum exercise in patients with severe COPD. In severe hypoxemic COPD patients such episodes are treated when long-term supplemental oxygen therapy is administered. Questions on the treatment of nocturnal oxygen desaturation should be directed toward those COPD patients whose daytime PaO_2 would not qualify them for home supplemental oxygen (PaO_2 ≥60 mmHg). Early detection and treatment of nocturnal hypoxemia in these patients seems clinically relevant since these feature can cause serious problems such as pulmonary hypertension, polycythemia and cardiac arrhythmia [1,2,3].

Since nocturnal studies are expensive, it is not feasible to perform in all mildly hypoxic or normoxic COPD patients, therefore many daytime parameters such as daytime SaO_2, $PaCO_2$, FEV_1, exercise test have been investigated to predict oxygenation during sleep in these patients [4, 5, 6, 7,8]. However, none of them has sufficient predictive values. The purpose of this study was to evaluate the relation between some daytime parameters which were day time blood gas values, spirometry, lung volumes, single breath CO diffusing capacity, maximum inspiratory (MIP) and expiratory (MEP) mouth pressures, SaO_2 during 6-min walk test, body mass index (BMI), skin fold thickness, handgrip force, high resolution computerized tomography (HRCT) and nocturnal oxygen saturation in stable COPD patients so that we could identify the group of patients who needed nocturnal studies.

Methods. Patient's with COPD who were under control in our outpatient clinic, participated in this study. ATS diagnosis criteria for COPD were used. Inclusion criteria were: daytime PaO_2 ≥60 mmHg, SaO_2 >90 mmHg, FEV_1 ≤ 70%. All patients were in a stable clinical condition and received optimal bronchodilator therapy. Patients were excluded if they had unstable angina, left heart failure, cirrhosis, diabetes mellitus, evidence of malignancy, bronchiectasis, receiving alcohol, psychotropic drugs or sedatives clinical features of obstructive sleep apnea (snoring, witnessed apnea or excessive daytime sleepiness), or evidence of an exacerbation in the preceding 3 weeks. Arterial blood was drawn from the radial artery with the patient in a seated position after resting for 15 minutes and breathing ambient air. Arterial blood gases were analyzed using a blood gas analyzer (ABL 5, Radiometer AS, and Copenhagen, Denmark). Static and dynamic lung volumes were measured using V-max 229 spirometry (Sensormedics, The Cardio Pulmonary Care Company, USA). Carbon monoxide diffusing capacity was measured by means of the single breath method. Maximal inspiratory and expiratory mouth pressures (MIP and MEP) were measured according to the method of Black and Hyatt .(9) At least three trials were completed by each participant with the goal of obtaining acceptable and reproducible results. Handgrip force was assessed as a measure of peripheral skeletal muscle strength. A handgrip dynamometer (Asimow Engineering Co., Los Angeles, CA 90024) was used to determine the isometric grasp in each hand by measuring the maximally developed strength of the flexors of the fingers. The mean value of left and right hand strength was used for statistical analysis. (10, 11) Nocturnal oxygen saturation was monitored throughout the night with finger probe by recordable pulse oxymeter (Profox Respironics Inc. Pittsburgh Pennsylvania). Recordings less than 6 hours were ignored. Baseline SaO_2 awake was defined as the mean saturation during the first 15 min of the recording with the patient supine and awake. Mean nocturnal SaO_2 was that until final morning wakening, including intervening periods of wakefulness. Minimum and maximum SaO_2, mean nocturnal saturation were analyzed by the Profox software. The SaO_2 values below 60% were ignored as being unreliable. Nocturnal desaturation was considered when there was a fall in oxygen saturation below 90% for 5 minutes and more. Epworth Sleepiness Scale was assessed. Patients having a scale value of six or more underwent sleep study. 6-minute walk test was performed to evaluate exercise capacity. Exercise desaturation was defined as a fall of ≥ 4% from the baseline value [7] Thorax HRCT was performed as close as possible in time to the pulmonary function tests. Images were acquired during inspiration

and expiration from lung apices to bases (1-mm collimation, 10-mm interval for inspiration or 30-mm interval for expiration, 560×560 matrix, high spatial frequency reconstruction algorithm). Images were reviewed at a window level of -700 and width of 1200. Abnormalities were characterized by a consensus of two radiologists who were unaware of the patient symptoms and physiological findings. According to CT findings, the patients were divided into two groups defining the presence of emphysema or chronic bronchitis.

Anthropometrical measurements: body height was measured to the nearest 0.5 cm with the patient standing barefoot. Body weight was measured to the nearest 0.1 kg with the patient in light clothing and without shoes. [12] Triceps skin fold thickness was measured with a fat calliper. Midarm muscle circumference was determined by measuring the overall midarm circumference with a soft tape midway between the shoulder and elbow. Body mass index was calculated by the formula weight (kg)/ height $(m)^2$.

Statistical analyze: Data were expressed as mean $\pm$ SD and range. Student t test was used to compare means between two groups. Correlation analyses were performed to identify relation between numeric variables. Pearson correlation coefficient was given in text. Stepwise multiple regression analysis was used to evaluate the contribution of various parameters in the prediction of mean nocturnal saturation.

A p-value of 0,05 or less was considered significant.

Results. We studied 41 patients. Six of them who had an Epworth Sleepiness Scale above six and snored at sleep underwent polysomnography. Three patients were excluded as they were found to have sleep-apnea syndrome. The characteristics of 38 patients (37 male, 1 female) whose nocturnal oxygen saturation were monitored are shown in Table 1.

Table 1 - Demographic, lung function and blood gases analyses data's of COPD Patients

	N	**Mean (SD)**	
	38	62.74 (7.99)	44-79
$Pa0_2$	38	72.87(9.11)	60-100
$PaCO_2$	38	41.71(6.62)	30-67
FVC%	38	77.18(17.96)	46-119
FEV_1	38	1275.89(435.47)	570-2510
FEV_1%	38	45.63(12.31)	19-70
	38	26.55(3.79)	17-33
Smoking*	38	51.71(31.41)	5-150
Htc	38	42.1(3.15)	36-51

BMI: Body mass index; Htc: Hematocrit. *: Package-year

All the patients were divided into two groups 'desaturators and nondesaturators' as previously defined (Table 2).

16 of 38 subjects desaturated during sleep, while the remaining were in nondesaturators group. There were significant differences between two groups in terms of DLCO%, SaO2, PaO2, FEV_1, FEV_1%, mean nocturnal oxygen saturation and baseline oxygen saturation. All these values were lower in desaturators.

There was no relation between the existence of chronic bronchitis and emphysema and nocturnal desaturation (p=0, 9).

We found correlation between 6-minute walk test and nocturnal desaturation (p=0,018). The positive predictive value of 6-minute walk test in determining nocturnal desaturation was 66% with a sensivity of 62% and specivity of 76%.

There was positive correlation between mean nocturnal saturation and PaO_2 (r=0,62, p=0,0001), SaO_2(r=0,65, p=0,0001), FEV_1 (r=0,37, p=0,02), FEV_1%(r=0,34, p=0,035), DLCO(r=0,41, p=0,011), DLCO% (r=0,32, p=0,049).

Table 2 - Comparison of desaturators and nondesaturators groups

	N	Mean (SD)	Mean (SD)	Mean (SD)	
Smoking *	38	52,3 (31,6)	58,3 (36,7)	48,1 (27,8)	0,3
$Pa0_2$	38	72,8 (9,1)	68 (5,9)	76,4 (9,4)	0,004
$PaCO_2$	38	41,7 (6,6)	44,1 (8)	39,9 (4,8)	0,054
SaO_2	38	94,1 (1,9)	92,9 (1,76)	94,9 (1,7)	0,001
FVC%†	38	77,1 (17,9)	73,1 (21,1)	80 (15,1)	0,2
FEV_1	38	1275 (435)	1087,5 (350)	1412,9 (446)	0,021
FEV_1%†	38	45,6 (12,3)	41,1 (11,6)	48,8 (12)	0,05
FEV_1/FVC	38	46,9 (8,6)	45,5 (8,6)	48 (8,7)	0,4
RV%†	35	162,8 (74,2)	171,2 (96,1)	156,5 (54,4)	0,5
TLC%†	35	108,6 (25)	111,2 (29,4)	106,6 (21,8)	0,6
RV/TLC	35	52,5 (14,1)	53 (17,8)	52,1 (10,9)	0,8
DLCO% †	38	67,4 (15,4)	64,5 (12,5)	69,5 (17,2)	0,3
MIP	38	88,0 (37,7)	82,6 (32,1)	92 (41,5)	0,4
MIP% †	38	81,9 (33,8)	80,8 (27,5)	82,7 (38,3)	0,8
MEP	38	116,6 (41)	122,4 (32,1)	112,4 (46,8)	0,4
MEP% †	38	58,4 (20,4)	64,1 (15,5)	54,3 (22,8)	0,1
HGF	32	345 (6,8)	32,6 (6)	36,3 (7,1)	0,1
BMI	38	26,5 (3,7)	26,4 (4,2)	26,6 (3,5)	0,8
TST	38	9,7 (5)	10,4 (5,4)	9,2 (4,9)	0,4
MAC	38	28,2 (3,1)	28,4 (2,7)	28,1 (3,4)	0,8
Total protein	38	7,3 (0,5)	7,17 (0,5)	7,4 (0,4)	0,1
Albumin	38	4,1 (0,5)	4 (0,5)	4,2 (0,4)	0,3
Mean nocturnal SaO_2	38	93,8 (2,0)	92,2 (1,8)	94,9 (1,2)	0,0001
Base SaO_2	38	94,7 (1,7)	93,5 (1,76)	95,5 (1,1)	0,0001
Epworth Scale	38	4 (3,3)	3,3 (2,3)	4,5 (3,9)	0,2
Htc	38	42,1 (3,1)	42,6 (4)	41,6 (2,1)	0,3

* package-year; † percentage of predicted; HGF: Handgrip force; TST: triseps skinfold thickness. ;MAC: Midarm circumference; Base SaO_2: Base oxygen saturation; Htc: Hematocrit

Stepwise multiple regression analysis showed that daytime SaO_2 was the only independent predictor of mean nocturnal saturation.

With further analysis, we observed no nocturnal desaturation in patients with day time SaO_2 >95% (sensitivity 100%, specificity 40% negative predictive value 100%) and PaO_2 > 80 mmHg (sensitivity 100%, specificity 31%, negative predictive value 100%) (Table 3). When we observed 92% and 93% as a cut off point for SaO2, negative and positive predictive values in determining nocturnal desaturators were 65%, 66% and 70%, 60% respectively. The predictive values are shown in table 3 for different cut off points of FEV_1 and DLCO in determining nocturnal desaturators. 69% of patients with a FEV_1> 1000 ml did not desaturate during sleep. 53% of patients whose DLCO %< 60% had nocturnal desaturation (Table 3).

Table 3 - Relation between nocturnal desaturation and SaO_2, PaO_2, FEV_1 DLCO%

	Desaturator	Nondesaturator	Positive Predictive value %	Negative Predictive value %
SaO_2 >% 95	0	9		100
SaO_2 ≤ %95	16	13	55	
	0	7		100
PaO_2≤80 mmHg	16	15	51	
FEV_1>1000 ml	8	18		69
FEV_1 ≤1000 ml	8	4	66	
DLCO% >60	9	16		64
DLCO% ≤60	7	6	53	

Discussion. In literature, there is no agreement in defining nocturnal desaturation. Little [7] and Heijdra [4] defined nocturnal desaturation as a fall >4% from awake baseline level for > 5 minutes while Block and Vos defined it only as a fall >4% and Baldwin as a fall >5%. [7,4,13,6] In the studies of Levi-Valensi and Gorecka patients were accepted to have nocturnal desaturation if SaO_2 was below 90% for a period of >30% of sleep time [5,16]. Fletchers definition was a fall below 90% for $\geq$ 5 minutes [5]. There has been no agreement about which definition has the greatest correlation with mortality and morbidity. On the other hand, in the double blind randomized study of Fletcher, desaturated patients were followed for three years and as a result, survival corrected by age was found to be significantly better in nondesaturators [17]. Because of this result, we used the definition of Fletcher's.

In our group SaO2, PaO_2, FEV_1, FEV_1% and mean nocturnal oxygen saturation were significantly lower in desaturators. Little et al. found positive correlation between mean nocturnal saturation and SaO_2, PaO_2, minimum exercise saturation and negative correlation with $PaCO_2$ [7]. In this study regression analysis revealed that daytime SaO_2 was the only independent predictor of mean nocturnal saturation. In our study, there was a positive correlation between mean nocturnal oxygen saturation and SaO_2, PaO_2, FEV_1, FEV_1%, DLCO, and DLCO% and with regression analysis, SaO2 proved to be the only independent predictor of mean nocturnal desaturation. With further analysis we observed on nocturnal desaturations in the patients with SaO_2>95% and PaO_2 > 80 mmHg. Fletcher et al. and Vos et al. also obtained similar results in their studies [5,6].

In stable COPD patients, $PaCO_2$ was proved not to be sufficient in predicting desaturators in many studies [4, 5, 6, 7]. In our study $PaCO_2$ did not correlate with mean nocturnal saturation, and there was no difference between desaturators and non-desaturators comparing $PaCO_2$.

The main mechanism causing nocturnal desaturation-especially during REM sleep- is periodic hypoventilation, which in turn is believed to be due to decreased activity of the intercostal and accessory muscles and reduced chemical respiratory drive. In COPD patients as the diaphragm strength and endurance may be affected by hyperinflation, increased airway resistance, and nutritional depletion, it may not compensate for the diminished activity of these muscles [18]. In patients with muscle weakness nocturnal oxygenation correlates with diaphragmatic strength [19]. It was therefore hypothesized by Heijdra et al. that a relation might exist between nocturnal arterial oxygenation and maximal inspiratory muscle strength in COPD patients [4]. In this study in which 34 patients with a mean FEV_1% 41, 7 % ±19, 9 were included, significant correlation was shown between this two parameters. However, MIP and MEP appeared to have a low predictive value. No correlations were found in other studies. In our study, we neither found correlation between mean nocturnal saturation and MIP nor there a difference between desaturators and nondesaturators in means of MIP and MEP as in the study of Little et al [7]. Therefore we do not recommend MIP and

MEP to predicting nocturnal desaturation.

FEV_1 is an important parameter in the diagnosis, fallow up, morbidity and mortality of COPD patients. COPD patients with a FEV_1< 1000 ml have greater mortality rates [20]. In the previous studies, FEV_1 was found to have no value in predicting nocturnal desaturation [5, 6, 7]. On the other hand in the study of Heijdra et al. FEV_1 was found to be one of the independent predictors. (4) In our study there was a difference between desaturators and non desaturators in means of FEV_1.With further observation when we used 1000 ml as a cut off point for FEV_1, only 66% of patients with a of FEV $_1$< 1000 ml suffered from nocturnal desaturation. However of FEV_1 had a low predictive value and this was confirmed by multiple regression analysis.

Exercise test desaturation had also been investigated in some studies. In the study of Little et al. where 6-minute walk test was used as in our study, a correlation had been found between minimum exercise oxygen saturation and mean nocturnal saturation but with a low predictive value [7]. Baldwin et al. also concluded that exercise studies added no extra information to awake blood gas analysis in predicting the likelihood of nocturnal oxygen saturation in COPD patients. (14) In our study, there was a correlation between exercise desaturation and nocturnal desaturation but only 66% of patients who desaturated during exercise were desaturators; we found that the predictive value of exercise testing for nocturnal desaturation was low.

Nutritional depletion can affect both peripheral skeletal muscle and respiratory muscle function [10, 20, 21]. In a study, positive correlation had been found between MIP and handgrip strength [11]. Therefore, we hypothesized that nutritional status could have effects on nocturnal oxygenation. We used body mass index, skin fold thickness, total protein and midarm circumference for nutritional assessment

We found no difference between desaturators and nondesaturators in terms of nutritional status parameters mentioned above and handgrip strength. There was also no correlation between this parameters and mean nocturnal oxygen saturation. On the other hand, in our study the patients were not severely undernourished. It is obvious that studies with more undernourished patients can better understand the relation between nutritional status and nocturnal saturation.

We conclude that daytime SaO_2 and PaO_2 is the best predictor of nocturnal saturation. Patients who have PaO_2 more than 80 mmHg do not need nocturnal saturation screening.

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