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Oral corticosteroids can improve nocturnal isolated hypoxemia in stable COPD patients with diurnal PaO_2 > 60 mmHg

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Abstract. – The aim of this study was to evaluate whether a short therapy cycle of oral methylprednisolone plus conventional therapy might improve isolated nocturnal hypoxemia evidenced through pulse-oxymetry in 28 patients (19 M/9 F; mean age 71 ± 8.31) with stable moderate to severe COPD (average FEV_1 of 43.33 ± 9.38 of theoretical) and daytime PaO_2 > 60 mmHg. All patients showed oxygen desaturation during the night and apnoea/hypoapnoea index ≤ 10, measured by means of a nocturnal polysomnography and were successfully on conventional treatment for COPD. The patients were randomly divided into two groups: 14 (steroid group) were administered methylprednisolone for three weeks at progressively decreasing doses (16 mg/die for the first 7 days, then 8 mg die for another 7 days, and finally 4 mg die for another 7 days) plus conventional therapy (bronchodilators and inhaled corticosteroids). The remaining 14 patients (control group) instead were on conventional therapy only. After 3 weeks for the steroid group, but no for the control group, was improved next parameters (p < 0.0001): VC (L) dropped from 2.53 ± 0.85 measured at baseline to 2.82 ± 0.84, FEV_1 dropped from 1.07 ± 0.31 L to 1.23 ± 0.31L, the IC dropped from 1.71 ± 0.48 to 2 ± 0.37L, the average nocturnal SpO_2% from 90.4 ± 1.79 to 92.3 ± 1.72 and the Nocturnal Time % of SpO_2 < 90% went from 31.19 ± 18.12 to 10.88 ± 11.56 after 3 weeks of therapy. Also dyspnoea, sleep duration and mean heart rate significantly improved (p < 0.0001). There was also a significant correlation between average increase in mean nocturnal SpO_2% and in Lowest SpO_2% and the variation in inspiratory capacity (IC) and in Sleep Duration % in the steroid group (p < 0.0001). In conclusion, methylprednisolone in combination with conventional medical therapy not only improved lung function values but also mean nocturnal oxyhemoglobin saturation and sleep duration in clinically stabilized COPD patients who experience nocturnal oxyhemoglobin desaturation.

Key Words:

COPD, Corticosteroid, Nocturnal SpO_2, Pulso-oxymetry

Introduction

Individuals with clinically stable chronic obstructive pulmonary disease (COPD), and with a PaO_2 when awake of > 60 mmHg, may experience nocturnal hypoxemia of different duration not associated with apnoea, especially during REM sleep[1-4]. Besides being characterized by bad quality of sleep, these episodes cause an increase in pulmonary arterial pressure, arrhythmias and in the long-term they are responsible for reduced survival[2,3]. In chronic obstructive pulmonary patients, the inflammation of the airways is responsible for broncho obstruction and it is found in clinically stable patients and in all degrees of severity of the disease[5-8]. Isolated incidents of nocturnal hypoxemia in these individuals are deemed to be related to a worsening of bronchial obstruction resulting from the nocturnal increase in bronchial tone caused by high cholinergic values[9]. Furthermore, bronchial obstruction is accompanied by a reduction in respiratory muscular activity with further worsening of alveolar hypoventilation and of the ventilation/perfusion ratio which is responsible for the nocturnal hypoxemia[2-3]. Extended treatment with

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anticholinergic agents in these patients may bring about a significant improvement in lung function with an increase in the mean nocturnal SaO_2 and in sleep quality[10,11]. In addition, a short cycle of steroid therapy (oral or inhaled) can reduce bronchial inflammation for COPD patients and at the same time improve bronchial airflow and the dyspnoea[12-18]. It is likely that by improving lung function this therapy may also have a positive repercussion on the episodes of nocturnal desaturation. The aim of this study is to determine whether a short cycle of oral steroid therapy (methylprednisolone) can bring about an improvement in isolated nocturnal hypoexemia measured with pulse-oxymetry in a group of patients with moderate to severe clinically stable COPD and with PaO_2 during the day > 60 mmHg.

Materials and Methods

Patients and Study Design

We recruited 28 patients (19 M/9 F; mean age 71 ± 8.31, range 50-80) affected by clinically stabilized moderate to severe COPD (mean FEV_1 % = 43.33 ± 9.38 of theoretical; range 55.03 to 23.8%) and with diurnal PaO_2 > 60 mmHg. They had significant oxyhemoglobin desaturation during sleep as shown through the preliminary polysomnographic tests performed to exclude the presence of the sleep apnoea syndrome. In order to be enrolled in the study, the selected patients were to have an apnoea/ipopnoea index ≤ 10 and an SpO_2 < 90% Time % greater than 10% of the total nocturnal recording time. All patients were former smokers (> 10 packs/year) aged > 40 and had been clinically stable for at least three months following optimal conventional medical therapy based on bronchodilators and steroid inhalation therapy, theophylline per os and in some cases also mucolytics, in accordance with the GOLD guidelines[17]. None of the patients had been on steroids per os during the three months prior to the study.

The recruited individuals were submitted to the following baseline tests: nocturnal pulse oxymetry, lung function tests, systemic arterial blood gas analysis; dyspnoea was evaluated using the Borg scale. Individuals were then randomly assigned to the steroid group and to the control group. Besides conventional therapy, at 8 a.m. the steroid group (20 pts) was given methylprednisolone at decreasing doses (16 mg/die for the first 7 days, then 8 mg die for another 7 days, and finally 4 mg die for another 7 days), while the control group (14 pts) was given the conventional therapy as mentioned above. After 3 weeks all the patients were again submitted to the tests run upon enrolment. Figure 1 summarizes the protocol of the study. All patients were duly informed and gave their consent.

Sleep Study

Before being enrolled, all the patients with a clinical and functional presentation of the COPD type, were submitted to a polysomnographic test using a portable "AlphaScreen" unit (Sensor Medics, Germany). The test was carried out at ambient conditions in the home of the patient. The unit records the oro-nasal airflow, the thoraco-abdominal movements, snoring, body position, saturation measurement and heart-rate. The recorded data were analysed using the "Jaeger Sleep Diagnostics" software. The apnoea/hypopnoea index was evaluated as well as the presence of isolated nocturnal hypoxemia (time % SpO_2 < 90% for more than 10% of the recording time), as a criterion for including or excluding patients from the study. The apnoea/hypopnoea index was expressed as the number of apnoea and hypopnoea episodes per hour of sleep.

Nocturnal pulse oxymetry was performed using a Minolta Pulsox 3ia unit (Minolta CO LTD, Japan). The sensor of the pulse oxymeter was fixed to the middle finger of the patient's right

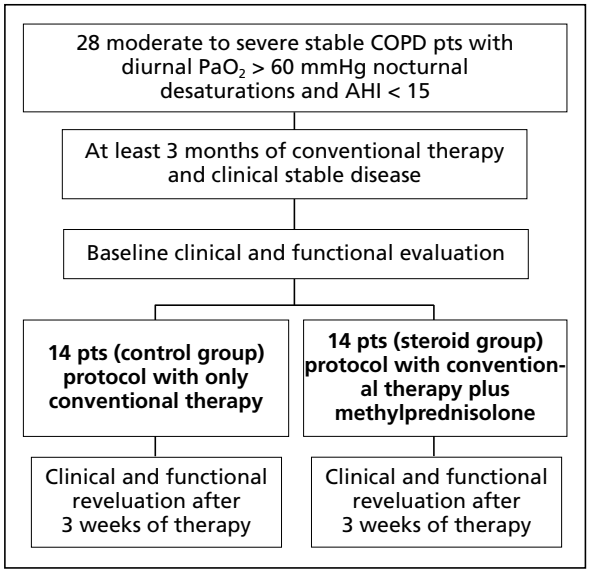

Figure 1. Protocol of the study.

hand and for all patients the measurements were taken between 10 p.m. and 7 a.m. The recordings were performed at ambient temperature in the patients' homes. The recorded data were analysed using the DS-3 software provided by the manufacturing company of the pulse oxymeter. For each measurement the following parameters were evaluated: the mean nocturnal SpO_2%; the time % $SpO_2 < 90$%, the time (minutes) $SpO_2 < 90$%, the lowest SpO_2%, means heart rate and maximum heart rate. Each patient was asked to indicate the total hours of sleep, and the Sleep Duration % was calculated on this basis (minutes of Total Time Sleep reported by the patient/minutes of Duration Time Registration × 100).

Lung Function Tests and Arterial Blood Gases

Lung function tests were carried out using the VMax 229 Pneumotachograph (Sensor Medics, Germany), connected to a personal computer to make the calculations and store the data. After suitable preparation, all patients underwent the slow and forced vital capacity manoeuvre in accordance with the guidelines[19]. The VC, FEV_1, and IC were evaluated at baseline and after three weeks of therapy, as envisaged in the study design in the two selected groups. All patients were submitted to the reversibility test using salbutamol (200 mcg by MDI). Improvement obtained after administering the bronchodilator was evaluated with respect to baseline values (pre-bronchodilator). The blood gas test was carried out at the time of recruitment of the patients in order to select those with a $PaO_2 > 60$ mmHg, and also at the beginning and at the end of the study so as to evaluate any variations in the PaO_2 and $PaCO_2$ obtained as a result of the therapy. Arterial blood samples were taken from the radial artery at ambient temperature and with the patient being at rest for at least 5 minutes. The unit used to read the results of the blood gas tests was the "AVL Omni 9, Austria".

Statistical Analysis

The program used for the statistical analysis, was the Primer, Bio-medical Statistics (Stanton A. Glantz, McGraw Hill Inc., New York, 1997). The measured data were expressed as mean and standard deviation. Student's *t* test was used to compare the data between different groups. Student's *t* test for paired data was used to compare the spirometric and nocturnal data measured at baseline and after 3 weeks of therapy in the two groups. The χ^2 test was performed to compare proportions between groups. The relationship between changes in functional and sleep parameters was assessed by the Pearson correlation coefficients. $p < 0.05$ was considered to be significant.

Results

All the data considered at baseline (anthropometric, lung function tests, clinical parameters and those obtained from the transcutaneous monitoring of SpO_2) were similar for the two groups of patients (Table I). The bronchodilation test using salbutamol showed a fair, albeit not significant, increase in FEV_1 in both groups ($p > 0.05$). Also conventional medical therapy used for controlling the symptoms related to the disorder included the same pharmaceutical products in both groups of patients (Table II).

In the control group, the statistical evaluation did not show up statistically significant differences when comparing the parameters measured at baseline and after 3 weeks of conventional therapy (Table I).

Instead, in the steroid group, treatment using methylprednisolone for 3 weeks in combination with conventional therapy determined a statistically significant improvement ($^*p < 0.0001$) in most parameters. In particular, after 3 weeks of steroid therapy, VC rose from 2.53 ± 0.85L (74.53 ± 17.38 of the theoretical value) to 2.82 ± 0.84L* (83.54 ± 16.43 of the theoretical value), the FEV_1 went from 1.07 ± 0.31L (42.74 ± 9.89 of the theoretical value) at baseline to 1.23 ± 0.31L* (49.86 ± 11.43 of the theoretical value), the IC rose from 1.71 ± 0.48L to 2 ± 0.37L*; the mean nocturnal SpO_2% increased from 90.4 ± 1.79 to 92.3 ± 1.72* (Figure 2) and the % Nocturnal Time $SpO_2 < 90$% dropped from 31.19 ± 18.12 to 10.88 ± 11.56*. After combination therapy with methylprednisolone, the patients in the steroid group found their dyspnoea to improve (Borg Scale) whose mean evaluation went from 2.64 ± 0.74 to 1.43 ± 1.01*, sleep duration % versus recording time went from 62.03 ± 8.17 to 71.4 ± 9.4*, mean cardiac pulse rate went from 77.43 ± 10.25 to 71.31 ± 9.8*. Moreover, in the steroid group the FEV_1/VC ratio was similar in the two steps of the study ($p > 0.05$).

Furthermore, in the steroid group was observed a significant correlation ($p < 0.05$) between nocturnal SpO_2% and Lowest SpO_2% in-

Table I. Parameters before and after conventional therapy (control group) or conventional therapy associated with methylprednisolone for 3 weeks (steroid group).

	Steroid group (14 pts)		Control group (14 pts)	
	Baseline	*After 3 weeks*	*Baseline*	*After 3 weeks*
Sex (M/F)	10/4	–	9/5	–
Age	72 ± 7.74	–	70 ± 9.02	–
BMI	26.6 ± 5.44	–	27.90 ± 4.8	–
AHI	5.64 ± 4.39	–	5.92 ± 3.05	–
ΔFEV_1 % after salbutamol	8.8 ± 5.3	–	8.76 ± 4.99	–
FEV_1 (L)	1,07 ±0.31	1.23 ± 0.31*	1.079 ± 0.25	1.11 ± 0.25
VC (L)	2.53 ± 0.85	2.82 ± 0.84*	2.64 ± 0.83	2.66 ± 0.75
IC (L)	1.71 ± 0.48	2 ± 0.37*	1.79 ± 0.42	1.84 ± 0.36
FEV_1/VC %	45.19 ± 15.24	45.9 ± 13.23§	42.95 ± 12.36	43.59 ± 11.79
Borg Scale	2.64 ± 0.74	1.43 ± 1.01*	2.78 ± 0.7	2.57 ± 0.64
PaO_2 (mmHg)	66.07 ± 6.08	72.8 ± 6.76*	66.32 ± 3.84	66.95 ± 2.69
$PaCO_2$ (mmHg)	48.1 ± 4.38	44.39 ± 4.58*	48.36 ± 4.26	48 ± 3.37
Cardiac pulse rate (bpm)	77.43 ± 10.25	71.31 ± 9.8*	78.75 ± 8.07	77.93 ± 8.7
Max Cardiac Pulse Peak	109.07 ± 12.06	101.71 ± 7.9°	112.85 ± 10.65	111.6 ± 10.32
Mean Nocturnal SpO_2%	90.4 ±1.79	92.3 ± 1.72*	89.98 ± 1.99	90.4 ± 1.7
Nocturnal Time $SpO_2 < 90\%$ (min.)	166.3 ± 95.31	60 ± 64.11*	172.5 ± 102.5	161.7 ± 86.25
%Nocturnal Time $SpO_2 < 90\%$	31.19 ± 18.12	10.88 ± 11.56*	31.81 ± 19.06	29.43 ± 17.42
Lowest SpO_2%	73.07 ± 11.51	79.28 ± 7.85°	70.07 ± 9.62	69 ± 9.67
TTR (minutes)	534.21 ± 31.13	546.9 ± 38.33§	546.6 ± 35.08	550.7 ± 27.02
Sleep duration %	62.03 ± 8.17	71.4 ± 9.4*	63.41 ± 10.56	65.4 ± 10.22

On baseline, functional parameters in Steroid group vs Control group: $p > 0.05$ (t test)
Control group: no statistically significant differences (paired t-test) comparing baseline vs after 3 weeks
Steroid group: $*p < 0.0001$, $°p < 0.01$, § $p > 0.05$ comparing baseline vs after 3 weeks (paired t test)
Sleep duration %: minutes of Total Time Sleep referred/minutes of Duration Time Registration × 100; BMI: Body Mass Index; AHI: Apnoea-Hypopnoea Index; VC: Vital Capacity; FEV_1: Forced Expiratory Volume one second; IC: Inspiratory Capacity; TTR: Total Time Registration; ΔFEV_1 % after salbutamol: % FEV_1 difference after 20 min from inhalation of 200 mg of salbutamol.

creases and variations of IC (r = 0.545 and r = 0.535 respectively) and Sleep duration % (r = 0.574 and r = 0.518 respectively) obtained following therapy as shown in Figure 3 and 4. Instead, in the control group no significant correlation ($p > 0.05$) was found between the Nocturnal SpO_2% and the variation in the other functional parameters that were measured.

Table II. Drugs administered to two COPD patient groups.

	Steroid group (14 pts)	Control group (14 pts)
β2-Agonists	14	13
ICS	12	13
Anticholinergics	13	14
Theophillines	8	9
Mucolytics	3	3

ICS: Inhaled Corticosteroids (Fluticasone, Budesonide, Beclometasone); β_2-Agonists: Formoterol, Salmeterol, Salbutamol; Anticholinergics: Tiotropium, Oxitropium, Ipratropium; Mucolytic: Acetylcysteine; Theophyllines: Theophylline, Bamifilline. Steroid group vs Control group: $p > 0.05$ ($\chi 2$ Test).

Discussion

These data highlight the fact that a short cycle of oral steroid therapy is capable of improving lung function and dyspnoea score in a group of clinically stable patients with moderate to severe COPD. The study also demonstrates that the improvement in lung function is matched with a considerable reduction in nocturnal hypoxemia events, a reduction in mean nocturnal cardiac pulse rate and a significant improvement in sleep duration.

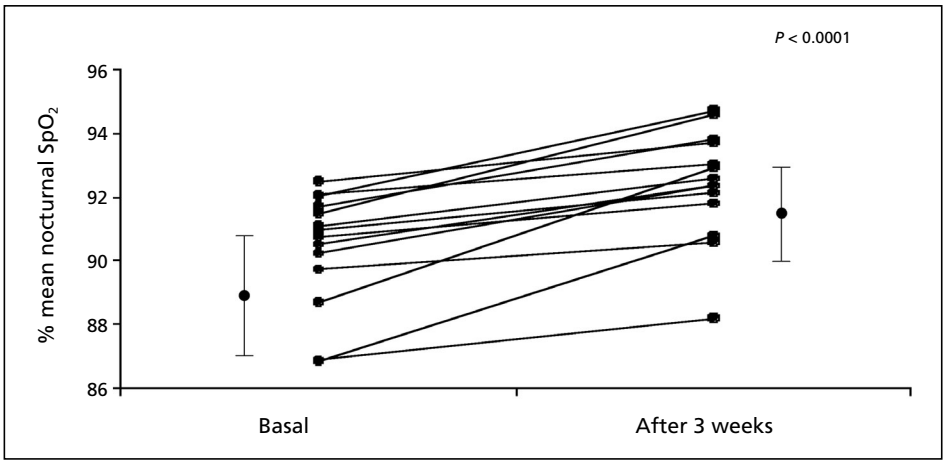

Figure 2. Nocturnal mean SpO_2% before and after conventional therapy associated with methylprednisolone for 3 weeks in patients steroid group (14 pts).

The improvement observed is likely due to the reduction in inflammation of the airways, resulting from steroid therapy. Inflammation is known to be present in increasing degrees of severity of the disease and it mainly affects the smaller airways[5,6,17]. Indeed, even in stable conditions, patients with severe COPD were found to have various inflammation markers in induced sputum and in the broncho-alveolar lavage[5-8] which are reduced appreciably both after inhaled steroid therapy[14,15,17] and after oral therapy[16-18]. Therefore, it is quite likely that the reduction in inflammation causes significant bronchodilation with a reduction in pulmonary hyperinflation. This is evidenced by the considerable increase in FEV_1 and in IC with the ensuing improvement in mean nocturnal SpO_2, in sleep quality and in mean and maximum nocturnal cardiac pulse rate.

Similar to our findings, recently a follow-up study of patients with severe emphysema submit-

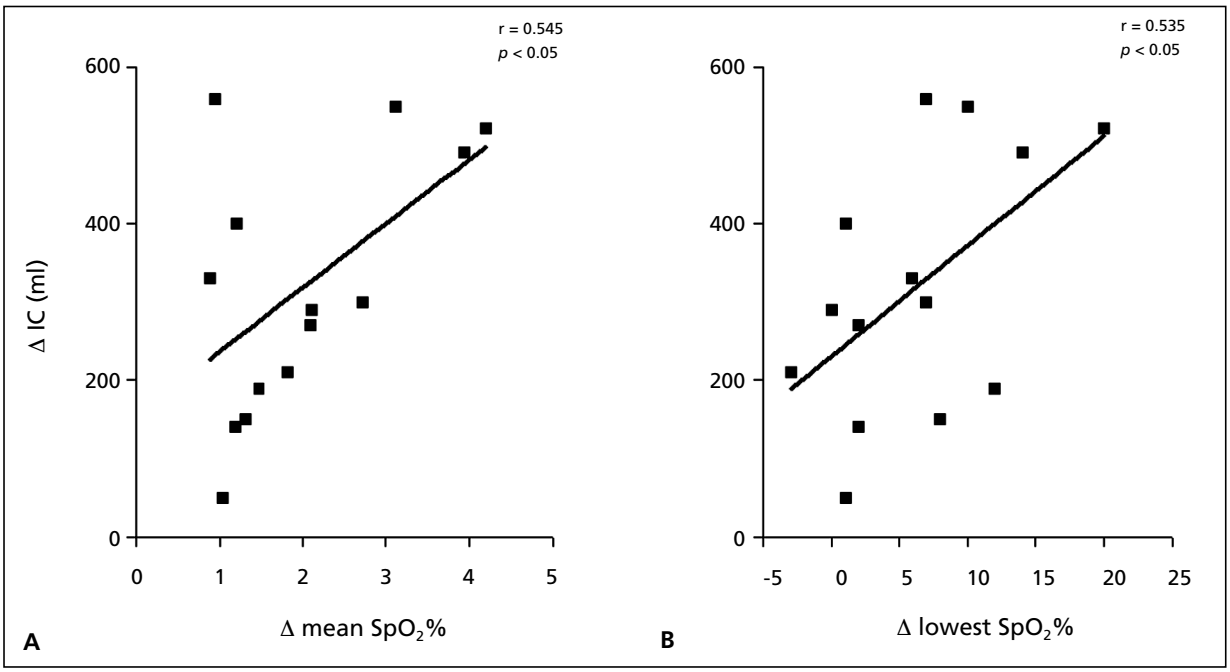

Figure 3. The relationship between IC increase (ml) and changes in nocturnal SpO_2% ***(A)*** and Lowest SpO_2% ***(B)*** obtained after Methylprednisolone in steroid group (14 pts).

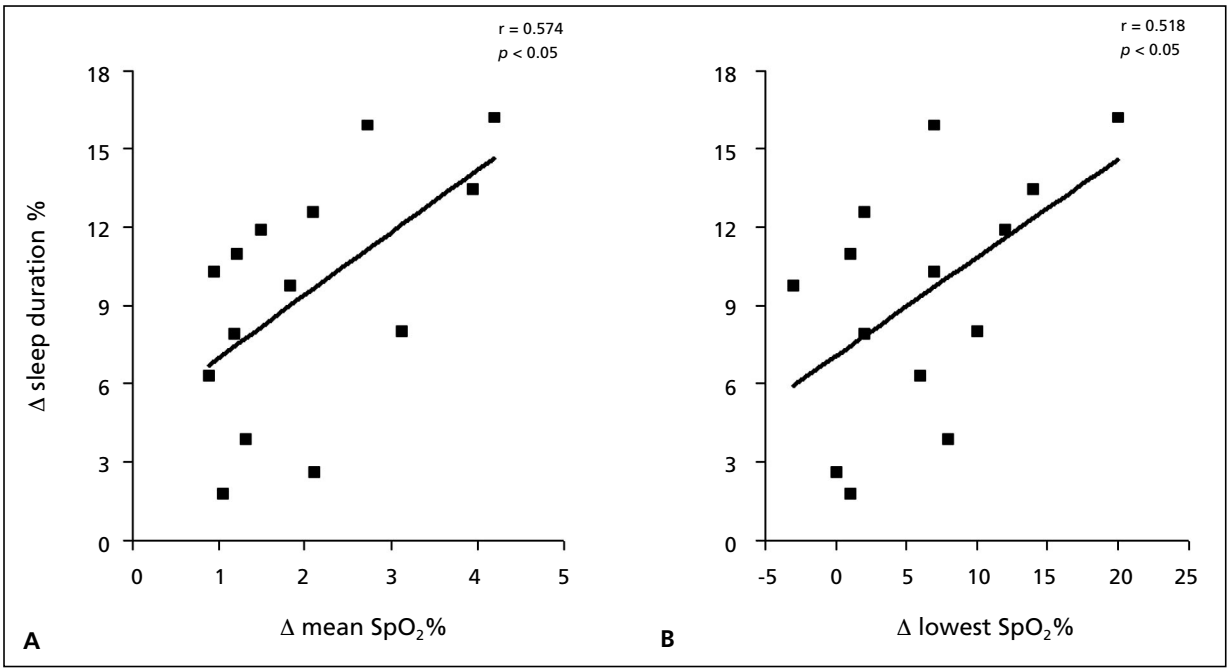

Figure 4. The relationship between Sleep Duration % increase and changes in nocturnal SpO_2% ***(A)*** and Lowest SpO_2% ***(B)*** obtained after Methylprednisolone in steroid group (14 pts).

ted to lung volume reduction showed that lung reduction brings about an increase in airflow, a reduction in lung hyperinflation and consequently an improvement in sleep quality and nocturnal oxygenation[20].

Also other studies claim that bronchial obstruction is among the factors that cause isolated nocturnal hypoxemia in COPD patients. These studies have found that a 4-week therapy with anticholinergic drugs (ipratropium or tiotropium bromide) or theophylline causes significant bronchodilation in COPD patients with isolated nocturnal desaturation with an ensuing improvement in mean nocturnal SaO_2 and in Sleep Quality[10,11,21,22]. It is therefore likely that the bronchial obstruction of the smaller airways sustained by bronchial inflammation is responsible for the alteration in the ventilation/ perfusion ratio in lung regions where the alveoli are hypoventilated hence causing a worsening in the gas exchange (hypoxemia and hypercapnia)[17,23,24]. During sleep it is likely that the decrease in breathing and the further increase in airway resistance linked to the increased bronchial tone further worsen alveolar ventilation and therefore the V/Q ratio[1-4,9].

In our study, the improvement in bronchial obstruction and in pulmonary hyperinflation obtained after steroid therapy probably induced an improvement in the V/Q ratio and in diaphragmatic function with a reduction in alveolar hypoventilation in some lung regions with the ensuing improvement in gas exchange both during the day and at night. This is confirmed by the significant correlation obtained between SpO_2 and lowest SpO_2 nocturnal variation and the difference in IC measured before and after steroid therapy; this is similar to what happens after lung volume reduction for lung emphysema or following bronchodilation therapy[10,11,20-22]. The improvement in nocturnal oxygen saturation is probably responsible for the reduction in mean and maximum nocturnal heart rate, which is evidence of improved pulmonary hemodynamics due to increase of oxygenation. In fact, it is known that oxygen administration as supplementary therapy for COPD patients is capable of reducing cardiac pulse rate as a result of a favourable and significant modulation of cardiac activity[27]. The better nocturnal oxygenation is probably responsible for the improvement in the sleep duration, according to with improvement of sleep quality obtained after surgical or bronchodilating therapy[10,11,20-22].

In COPD individuals with nocturnal desaturation versus patients that are not desaturated, high

endothelin-1 (ET-1) levels have been found both during the day and at night. This cytokine has a bronchoconstriction and vasoconstriction action that increases pulmonary arterial pressure[26] and can thus alter the V/Q ratio also in well ventilated pulmonary regions. Steroid therapy probably reduces the ET-1 levels and consequently improves pulmonary arterial pressure[27,28] and the V/Q ratio through vasodilation and bronchodilation, with positive repercussions on gas exchanges.

As is well known, as a consequence of the normal circadian rhythm, during sleep there is an increase in the cholinergic tone which causes a reduction in the size of the airways with respect to the daytime[9,29]. It is likely that steroid replacement therapy may influence a drop in cortisol during the night and thus improve lung function during sleep with positive repercussions on nocturnal desaturation.

In conclusion, in clinically stable moderate-to-severe COPD patients who have significant nocturnal desaturation episodes, the administration of methylprednisolone in combination with optimal conventional therapy has proven to be effective in improving sleep duration and nocturnal oxygenation. The ensuing improvement in nocturnal SpO_2 correlates with the functional improvement in breathing thus suggesting also a bronchial mechanism in causing the isolated hypoxemia episodes in COPD patients.

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