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Short term effect of a single dose of formoterol or tiotropium on the isolated nocturnal hypoxemia in stable COPD patients: a double blind randomized study

B. SPOSATO, C. FRANCO

UOC Pneumologia, Azienda Ospedaliera "Misericordia", Grosseto, Italy

Abstract. – Patients with stable chronic obstructive pulmonary disease (COPD) and diurnal PaO_2 > 60 mmHg may have transient oxygen desaturation during sleep. The effect of bronchodilators on nocturnal hypoxemia is not known. The aim of this study was to evaluate if a single dose of Formoterol or Tiotropium, administered in the evening, could improve nocturnal hypoxemia in patients with stable middle/severe COPD. Thirty-seven patients (25 M/12 F; mean age 68.97 ± 8.57, range 50-78; mean FEV_1% of predicted 46.29 ± 9.2) with PaO_2 > 60 mmHg, but with significant oxygen desaturation during sleep and apnea/hypopnea index ≤ 10 were selected. They randomly underwent three consecutive nocturnal pulsoxymetry: baseline and after taking placebo and 12 µg of Formoterol (20 pts) or 18 µg of Tiotropium (17 pts) in the evening. FEV_1 and IC, measured after 1 h of taking bronchodilators, were significantly higher than placebo. The variation, with regards to baseline values, in mean heart rate and Lowest SpO_2% measured after Tiotropium (-1.68 ± 4.01 and 3.23 ± 8.58 respectively) was higher ($p < 0.05$) than placebo (-0.108 ± 2.85 and 0.29 ± 7.05 respectively). Moreover, the trend time of SpO2% (measured by pulse-oximeter at each hour of total time registration) after Tiotropium was significantly higher than baseline or placebo ($p < 0.01$). Instead, the trend time of SpO_2% after Formoterol, except for an initial transient hypoxemia fall, was similar to baseline condition and after placebo. Also the trend time of heart rate resulted significantly lower in the Tiotropium group, but higher in the Formoterol group. In conclusion, Formoterol does not seem to influence the nocturnal hypoxemia in stable COPD patients probably for the worsening V/Q ratio. On the contrary, a single dose of tiotropium seems to decrease the severity in the nocturnal desaturations in stable COPD patients probably due to the reduction in the nocturnal bronchial colinergic tone.

Key Words:

COPD, Formoterol fumarate, Tiotropium bromide, Nocturnal hypoxemia, Sleep.

Introduction

The recent guide-lines for management of chronic obstructive pulmonary disease (COPD) recommend the use of regularly scheduled treatment with long-acting bronchodilators in a mild to a very severe disease. This therapy can determine a significant bronchodilation and improves quality of life, dyspnoea perception and exercise performance. Furthermore regular use of bronchodilators may reduce the number of exacerbations[1-3]. Formoterol fumarate and tiotropium bromide are new selective compounds which have a sustained and long lasting bronchodilator effect (about 12 h and 24 h respectively) and are able to reduce lung hyperinflation in COPD patients with a stable disease[4-7].

Moreover, it is known that the inhalation of β_2-agonists by patients with airway obstruction often results in a transient decrease in arterial oxygen tension (PaO_2), despite concomitant bronchodilation[8-13], due to a worsening of ventilation/perfusion ratio[14-18]. In contrast, anticholinergic bronchodilators have been shown to have a relatively small effect on arterial blood gases in both stable or in acute exacerbation of COPD[8,11-13,17,19].

During sleep, especially during rapid eye movement (REM) sleep, episodes of oxigen desaturation occur in several COPD patients with

Corresponding Author: Bruno Sposato, MD; e-mail: bsposat@tin.it

stable disease and diurnal PaO_2 > 60 mmHg[20-22]; this is due to alveolar hypoventilation and ventilation/perfusion mismatching. The effect of bronchodilators on the nocturnal hypoxemia in COPD patients is not well known. Nocturnal increase in bronchial tone, caused by high cholinergic value[23], could determine an increasing airflow obstruction[24]. As a consequence, this might cause a worsening of the ventilation/perfusion ratio, which is responsible for nocturnal hypoxemia in COPD patients[20-23]. It is likely that the improvement of airflow obstruction, subsequent to inhaled bronchodilators, may have a positive repercussion on the episodes of nocturnal desaturation. In fact, the four-week-treatment with anticholinergic (Ipratropium or Tiotropium) or theophilline improves lung function, nocturnal SaO_2% and sleeping quality in COPD patients[25-28]. No studies have assessed the effect of the β_2-agonists on the nocturnal oxygen desaturation in patients with COPD. The aim of this study was to evaluate if a single evening dose of formoterol or tiotropium can also produce an improvement in isolated nocturnal hypoxemia, measured with pulse-oximetry in a group of patients with moderate to severe stable COPD and diurnal PaO_2 > 60 mmHg.

Materials and Methods

Patients and Study Design

We selected 37 patients (25 M/12 F; mean age 68.97 ± 8.57, range 50-78) affected by moderate-severe stable COPD[2] (mean FEV_1% of predicted 46.29 ± 9.2; range 56.63 to 30.22 %) and diurnal PaO_2 > 60 mmHg, but with significant oxyhemoglobin desaturation during sleep as shown through the preliminary complete nocturnal cardiac-respiratory monitoring test performed to exclude Sleep Apnea Syndrome. In order to be enlisted in the study, the selected patients were to have the following characteristics: apnoea/ipopnoea index (AHI) ≤ 10 and Time % SpO_2 < 90% 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. The above mentioned patients assumed optimal conventional medical therapy (inhaled corticosteroids and bronchodilators, theophylline per os and in some cases also mucolytics) according to the GOLD guidelines[2]. During the 3-month-period prior to the study, none of the patients had been on steroids. Patients were excluded if receiving a regular oxygen therapy or showing asthma, athopy, cardiac arrhythmia and/or heart failure, symptomatic urinary outflow obstruction, narrow-angle glaucoma. Moreover, they were excluded if showing exacerbation of disease in the preceding 3 months. Patients were asked not to consume coca-cola, coffee or tea before and during the investigation. The selected patients were divided in two groups in a randomized and double-blinded fashion: group F (20 pts) and group T (17 pts). The former group performed the protocol with formoterol, while the latter with tiotropium. All patients performed nocturnal pulse-oxymetry after 48 hours from the suspension of the inhaled bronchodilators. Subsequently, they performed spirometry and a bronchodilator reversibility test after 60 minutes to inhaling Placebo, Formoterol or Tiotropium. After the reversibility tests the 2 groups of patients underwent 2 consecutive pulse-oxymetry after the evening inhalation of Placebo, Formoterol or Tiotropium. Protocol is summarized in Figure 1. Salbutamol, if necessary, was withheld for 6h before the lung function test and pulse-oxymetry. On selection, they also performed arterial blood gas analysis and Borg dyspnoea scale. Informed consent was obtained from all patients.

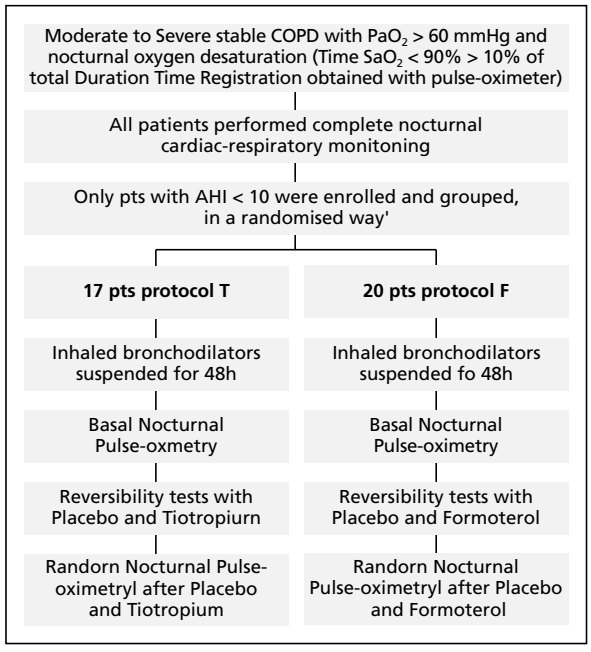

Figure 1. Protocol of study.

Sleep Study

All patients underwent a complete nocturnal cardiac-respiratory monitoring test, before being enrolled using a portable "AlphaScreen" unit (Sensor Medics Germany). The test was carried out while the patient was breathing room air at home. The unit recorded the oro-nasal airflow, 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, as a criterion for including or excluding patients from the study. Only patients with AHI ≤ 10 and Time % SpO_2 < 90% for more than 10% of the recording time were selected for 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 hand and for all patients the measurements were taken between 10 p.m. and 7 a.m. The recordings were carried out while the patient was breathing room air at home. The recorded data were analysed using the DS-3 software provided by the manufacturing company of the pulse oxymeter. The following parameters were evaluated for each measurement: mean nocturnal SpO_2%, Time % SpO_2 < 90%, Time (minutes) SpO_2 < 90%, Lowest SpO_2%, mean and maximum heart rate. The trend of nocturnal SpO_2% and heart rate in the 2 selected groups were marked using the values of SpO_2 and heart rate measured at each hour of nocturnal registration. Each patient was asked to indicate the total hours of sleep. 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). After suitable preparation, all patients underwent the slow and forced vital capacity manoeuvre in accordance with the guidelines[29]. The VC, FVC, FEV_1, and IC were evaluated at baseline and 60 minutes after administering Formoterol or Tiotropium and Placebo, as envisaged in the study design in the two selected groups. The improvement obtained after administering the bronchodilator was evaluated with respect to baseline values (pre-bronchodilator). Either Formoterol (12 µg), Tiotropium (18 µg) or Placebo were given in powder form for inhalation by the device "Autohaler" in Group F and "HandiHaler" in Group T. The blood gas test was carried out on selection of the patients in order to select those with a PaO_2 > 60 mmHg. This test was also done at the beginning and at the end of the study to evaluate any variations in the PaO_2 and $PaCO_2$ obtained after therapy. Arterial blood samples were taken from the radial artery, without oxygen-therapy and with the patient being at rest for at least 5 minutes. The unit which was 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 shown data were expressed as mean ±SD. Student's t test per paired data was used to compare the spirometric and nocturnal data measured before and after bronchodilator and placebo in the two groups. The analysis of variance was used to compare the spirometric and nocturnal data measured at baseline and after bronchodilator and placebo between the two groups. The comparison in the nocturnal trend of SpO_2 and heart rate, in the different experimental conditions, was carried out with the use of ANOVA test for repeated measures. The relationship between changes in functional and sleep parameters was assessed by linear regression and Pearson correlation coefficients. $P < 0.05$ was considered to be significant.

Results

Functional data obtained from the two groups are shown in Table I. No differences were observed in the two groups. FEV_1 and IC increase obtained after Formoterol (139.5 ± 70.52 and 271.5 ± 177.4 ml respectively) and Tiotropium (152.9 ± 79.59 and 284.1 ± 168.9 ml respectively) were similar, but clearly higher than after placebo (Figure 2). No differences were observed between basal and after bronchodilator of nocturnal parameters, measured with pulse-oxymetry in and between the two groups (Table

Table I. Patients' characteristics in the two groups considered.

	Group F (20 pts)	Group T (17 pts)
Sex (M/F)	14/6	11/6
Age	69.4 ± 8.82	68.47 ± 8.5
BMI	28.08 ± 4.26	29.38 ± 4.53
AHI	6.9 ± 2.49	6.41 ± 3.26
FEV1 (L)	1.13 ± 0.3	1.14 ± 0.24
FEV1%	45.22 ± 9.53	47.5 ± 8.91
FVC (L)	2.07 ± 0.53	2.06 ± 0.79
FVC%	63.7 ± 12.99	64.15 ± 15.04
VC (L)	2.47 ± 0.68	2.43 ± 0.83
VC%	73.6 ± 16.57	75.2 ± 17.16
IC (L)	1.8 ± 0.37	1.79 ± 0.41
FEV_1/VC%	46.9 ± 13.7	49.4 ± 15.46
Borg Scale	2.25 ± 1.07	2.05 ± 0.74
PaO_2 (mmHg)	65.96 ± 5.99	66.7 ± 5.82
$PaCO_2$ (mmHg)	47.86 ± 4.37	47.97 ± 3.96

No differences between two groups (t-test)
BMI: Body Mass Index; AHI: Apnea-Hypopnea Index; IC: Inspiratory Capacity.

II). On the contrary, the analysis of differences in nocturnal parameters, with respect to the basal values, shows how the variation of mean heart rate and of Lowest SpO_2% measured after tiotropium (-1.68 ± 4.01 and 3.23 ± 8.58 respectively) were significantly higher ($p < 0.05$) than placebo (-0.108 ± 2.85 and 0.29 ± 7.05 respectively; Table III). Whereas, in group F, no difference was revealed between variations obtained after placebo and formoterol (Table III).

The nocturnal trend of SpO_2% in group F was similar in the 3 conditions: baseline, after placebo and formoterol ($p > 0.05$); Figure 3). But the value of SpO_2% measured at 11.00 p.m., after inhalation of formoterol, resulted significantly lower ($p < 0.05$) in comparison to the same value measured at the same time in baseline and placebo conditions (Figure 3). The nocturnal trend of SpO_2 in group T, after administering tiotropium, it was significantly higher ($p < 0.01$) in comparison to baseline and placebo (Figure 4). In group F, the trend of the nocturnal curve for heart rate was higher after inhalation of formoterol than baseline and placebo (Figure 5; $p = 0.05$). But, in group T the heart rate curve lies on a lower level after tiotropium compared to baseline and placebo conditions ($p < 0.05$; Figure 6). A positive significant relationship was found between the variation (as regards to basal values) of Lowest SpO_2% and the increase of FEV_1 ($r = 0.71$; $p < 0.01$) and IC ($r = 0.61$; $p < 0.05$) obtained after the evening administering of Tiotropium (Figure 7 A and B). This could mean that a lung function improvement coincides with a smaller severity of nocturnal hypoxemia. Moreover, a negative significant relationship was found between the variation of the Lowest SpO_2% and the variation of the maximum heart rate ($r = -0.63$; $p < 0.05$), obtained after inhalation of Tiotropium (Figure 7 C). This could mean that an improvement of the severity of nocturnal hypoxemia coincides with a reduction of the heart rate.

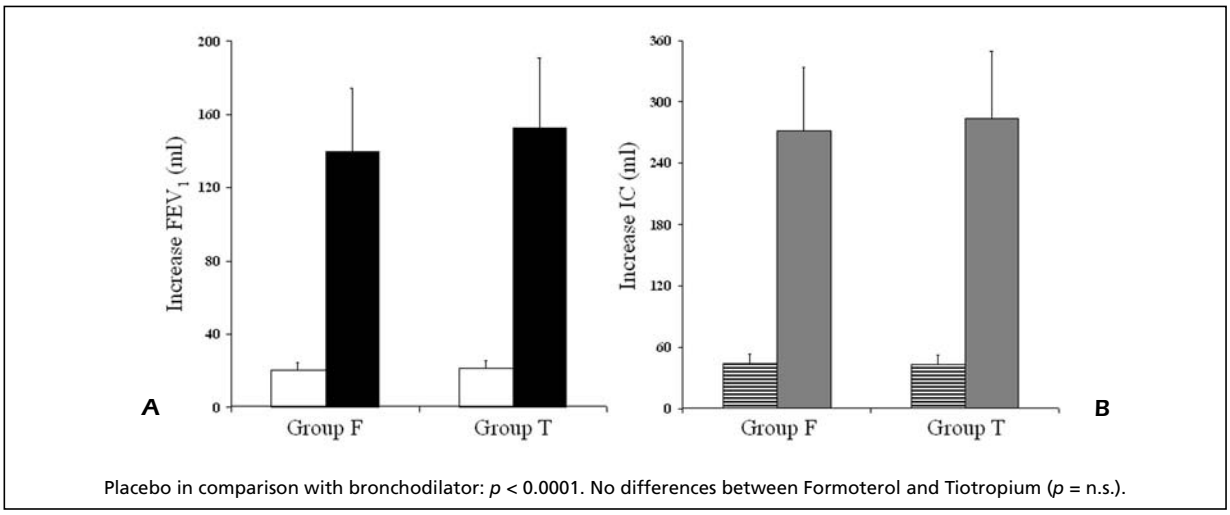

Figure 2. Increase (ml) of FEV_1 ***(A)*** and IC ***(B)*** obtained after 60 minutes of Formoterol (12 μg), or Tiotropium (18 μg) and placebo inhalation.

Table II. Nocturnal functional parameters measured by pulse-oximeter in basal condition and after placebo and Formoterol (Group F) or Tiotropium (Group T) inhalation.

	Group F			Group T		
	Basal	*Placebo*	*Formoterol*	*Basal*	*Placebo*	*Tiotropium*
Cardiac pulse rate (bpm)	77.28 ± 9.38	77.43 ± 7.75	78.65 ± 7.09	77.83 ± 8.17	77.7 ± 7.39	76.14 ± 6.55
Max Cardiac Pulse Peak	109.5 ± 10.08	110.55 ± 10.4	113.2 ± 10.23	110 ± 7.94	110.8 ± 11.28	108.05 ± 7.7
Mean Nocturnal SpO_2%	89.8 ± 1.74	89.9 ± 1.8	90 ± 2.24	90.2 ± 2.05	90.4 ± 1.9	90.81 ± 2.43
Nocturnal Time SpO_2 < 90% (min.)	189.5 ± 115.9	191.5 ± 105.9	188.3 ± 132	179.3 ± 113.1	180.7 ± 99.38	158.5 ± 128.15
%Nocturnal Time SpO_2 < 90%	35.11 ± 20.56	35.4 ± 19.6	35.23 ± 23.39	32.3 ± 20.65	32.8 ± 18.13	29.24 ± 23.9
Lowest SpO_2%	70.5 ± 11.02	70.75 ± 8.74	71.4 ± 9.87	70.82 ± 10.91	71.1 ± 9.09	74 ± 9.6
TTR (minutes)	549.1 ± 28.82	537.5 ± 17.97	546.3 ± 30.85	558.4 ± 22.52	546 ± 15.03	545.76 ± 18.08
Sleep duration %	63.14 ± 8.61	64.16 ± 8.35	64.87 ± 8.33	62.33 ± 8.32	63.09 ± 6.72	65.68 ± 9.68

No differences in and between groups (paired *t* test and analysis of variance). TTR: Total Time Registration.

Discussion

The aim of this study was to evaluate if formoterol and tiotropium, in comparison to the placebo, could have an effect on the nocturnal hypoxemia in COPD patients with oxygen desaturation during sleep. A single dose of Formoterol, in spite of its effects on the bronchodilatation and reduction of hyperinflation, seems ineffective on the length and severity of nocturnal hypoxemia. However, 2 hours after formoterol inhalation (11:00 p.m.), the analysis of the SpO_2 trend shows a lower SpO_2 value in comparison to placebo or to the basal levels. In the following hours, the SpO_2% trend remained similar to the placebo and to the basal levels. This could agree with other studies that have described a transient decrease in oxygen tension in arterial blood (PaO_2) after administering β_2-agonists to patients with airway obstruction[8-13]. The hypoxemia during sleep in COPD patients seems to be caused by alveolar hypoventilation and worsening of the V/Q ratio by an increase of the airway resistance and a reduction in the FRC for supine position[20-23]. It is probable that Formoterol causes a worsening of the V/Q ratio with a larger fall of the SpO_2, especially during the first hours following its administering. The worsening of the V/Q ratio due to the β_2-agonists could be in relation to a vasodilatation of the lung circulation, because of the existence of β-adrenergic receptors on the wall of the lung arterioles[14-18]. This causes a subsequent shunt of the blood flow towards poorly ventilated lung regions[14-18]. However, it is also probable that the temporary fall of SpO_2 at the beginning of the recording could be provoked by the supine position. Some Authors have shown how the fall in oxygen tension in ar-

Table III. Comparison between variations, as regards to baseline values, of the nocturnal parameters measured by pulse-oximeter after placebo and Formoterol (Group F) or Tiotropium (Group T) inhalation.

	Group F		Group T	
	Placebo	*Formoterol*	*Placebo*	*Tiotropium*
Cardiac pulse rate (bpm)	0.15 ± 5.7	1.37 ± 6,78	-0.108 ± 2.85	-1.68 ± 4.01*
Max Cardiac Pulse Peak	1.05 ± 6.92	3.7 ± 9.9	0.82 ± 9.27	-1.94 ± 6.95
Mean Nocturnal SpO_2 %	0.094 ± 1.01	0.196 ± 1.52	0.065 ± 0.8	0.52 ± 1.34
Nocturnal Time SpO_2 < 90% (min.)	2 ± 54.77	-1.15 ± 75.72	1.29 ± 42.6	-20.76 ± 73.13
%Nocturnal Time SpO_2 < 90%	0.335 ± 11.59	0.122 ± 14.8	0.59 ± 7.81	-3.08 ± 12.39
Lowest SpO_2 %	0.25 ± 4.86	0.95 ± 5.05	0.29 ± 7.05	3.23 ± 8.58*
Sleep duration %	1.24 ± 6.87	1.73 ± 7.18	1.13 ± 6.7	3.35 ± 8.5

*$p < 0.05$: Tiotropium in comparison with placebo in Group T.

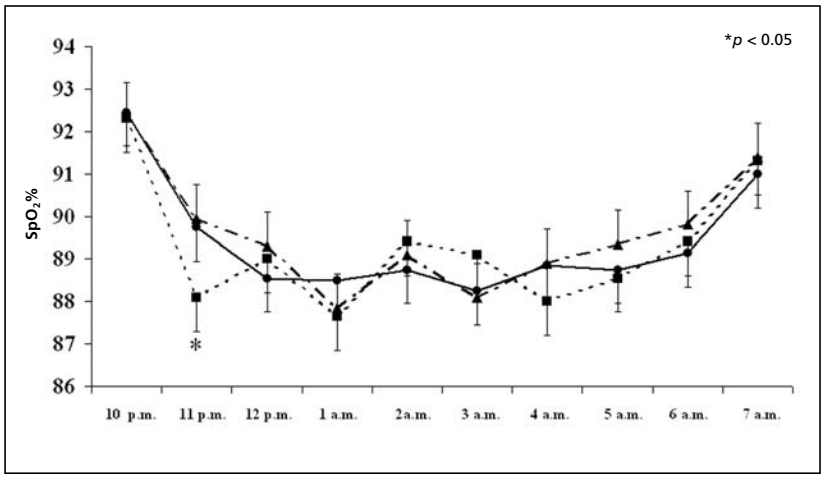

Figure 3. Nocturnal curve time of SpO_2% measured by pulse-oximeter at each hour of total time registration in baseline condition (•), after placebo (▲) and Formoterol (■) inhalation. No difference between curve time of formoterol, baseline and placebo.

terial blood, after the Salbutamol inhalation, was evident only if the patient had a supine position; no fall in oxygen tension in arterial blood was shown if the patient was seated[9]. In our study, the significant reduction of the SpO_2, obtained at the 2nd hour of recording after Formoterol, seems to be limited only to that hour. In fact, it disappears in the following hours. This could match with other studies which show a temporary hypoxemic effect (limited to a few hours, from 1 to 3 hours) after the β_2-adrenergic administering[8,10,12,18] in the daytime. It is therefore plausible that administering Formoterol 3-4 h before lying down for the night could avoid this effect. The trend of nocturnal heart rate after inhalation of Formoterol was significantly higher with regards to baseline and placebo conditions. This agrees with other studies that have observed an increase in heart rate after inhalation of β_2-agonists, probably due to cardiac β-adrenergic receptor stimulation[13,18,30-32]. Moreover, this effect can be further magnified by the nocturnal hypoxemia of these patients[31]. Likely the increase in heart rate after β_2-agonists inhalation could also determine an increase in cardiac output; this factor does not favour the improvement of oxygenation[30].

On the contrary, Tiotropium determines an improvement in the Lowest SpO_2 and a reduction in the mean heart rate if compared to baseline and placebo.The improvement in the Lowest SpO_2 and the time-trend of nocturnal SpO_2 seems to be related to the improvement in the lung function following bronchodilator administering. This is demonstrated by a significant correlation between Lowest SpO_2 and the increase in FEV_1 and IC, measured after Tiotropium administering.

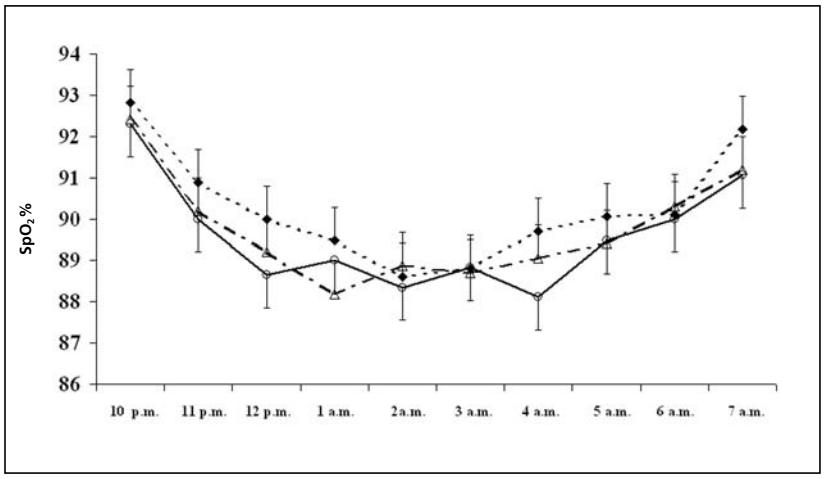

Figure 4. Nocturnal curve time of SpO_2% measured by pulse-oximeter at each hour of total time registration in baseline (○) condition, after placebo (Δ) and Tiotropium (◆) inhalation. Tiotropium curve time is significantly higher in comparison with baseline and placebo ($p < 0.01$).

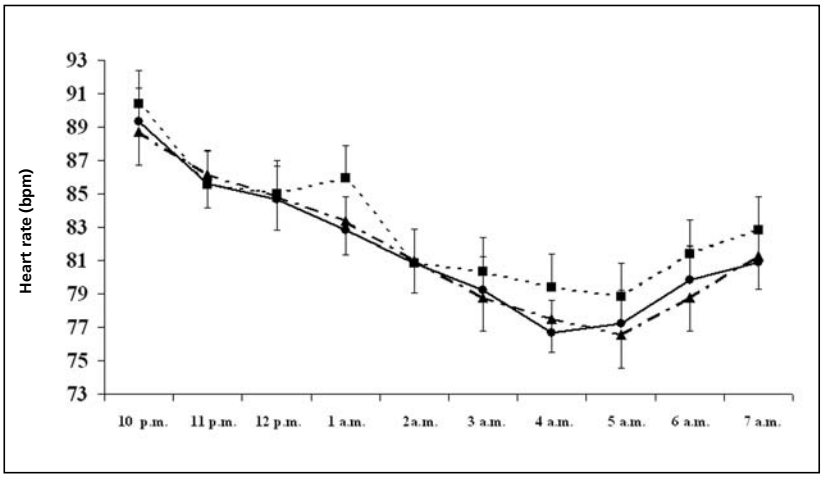

Figure 5. Nocturnal curve time of heart rate (bpm) measured by pulse-oximeter at each hour of total time registration in baseline (•) condition, after placebo (▲) and Formoterol (■) inhalation. Formoterol curve time is significantly higher in comparison with baseline and placebo ($p = 0.05$).

The hour by hour trend of the SpO_2 and the mean heart rate during the night-time is better (statistically significant) if compared to the basal and to the placebo. Unlike β_2-agonists, several Authors who evaluated daytime oxygen (by Blood Gas Analysis) following anticolinergic inhalation, did not observe any significant hypoxemic effect[8,12,13,19]. However, some Authors[11] in a recent study in which they evaluated the effect of Tiotropium on the gas exchange, found a small (even if very small) decrease in the daytime PaO_2 after the drug inhalation. Nevertheless, this decrease resulted smaller than the decrease observed by Formoterol and Salmeterol. No explanation was given by the authors.

Others confirmed an important improvement in the nocturnal SaO_2 after a regular 4 week therapy with Ipratropium or Tiotropium[25,26], related to the functional improvement obtained after the treatment[25]. This improvement, after tiotropium, may be due to the capability of the anticolinergics to decrease the nocturnal colinergic tone, which increases during the night according to the circadian rhythm[23,24]. In fact, the FEV_1 measured during the night hours in COPD patients, demonstrated a progressive worsening until it reached minimal levels during the first hours of the morning[24]. In these patients, administering tiotropium in the morning or in the evening produces an important improvement in FEV_1 in the night hours, even if it does not suppress the normal circadian rhythm[24]. This result matches our study. In fact, in our sample, the SpO_2, in baseline and placebo conditions, gradually decreases

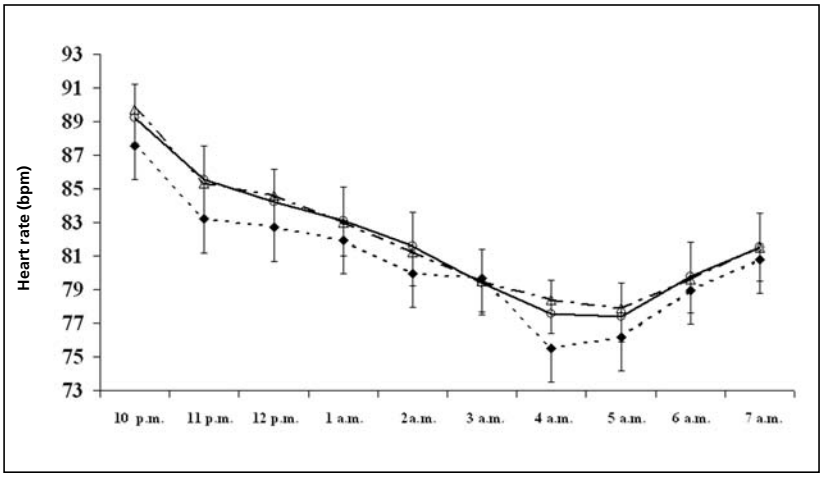

Figure 6. Nocturnal curve time of heart rate (bpm) measured by pulse-oximeter at each hour of total time registration in baseline condition, after placebo and Tiotropium inhalation. Tiotropium curve time is significantly lower in comparison with baseline and placebo ($p < 0.01$).

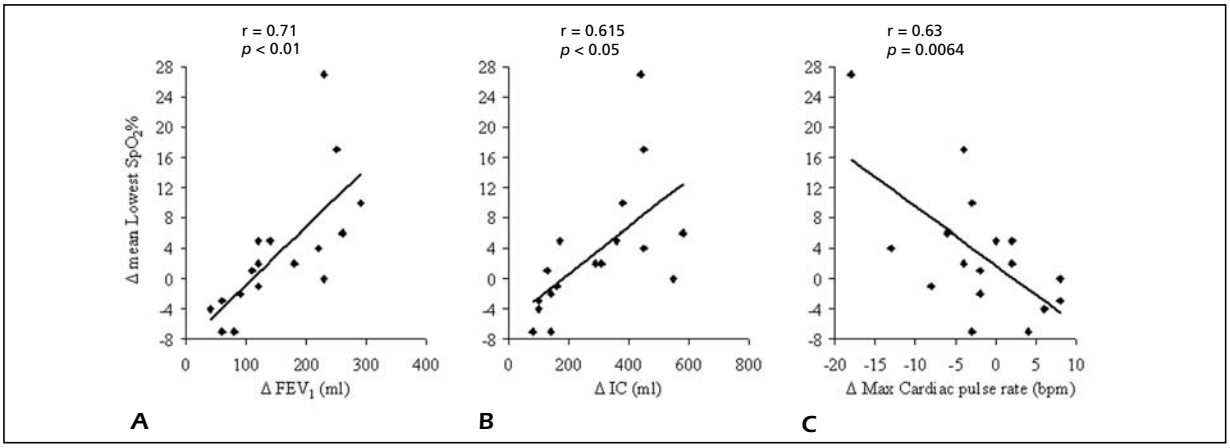

Figure 7. Relationship between the variation in the Lowest SpO_2% and differences (ml) in the FEV_1 ***(A)*** and IC ***(B)*** and maximum cardiac pulse rate ***(C)*** obtained after a single dose of Tiotropium (Group T).

reaching the lowest level in the early hours of the morning. This SpO_2 trend is comparable to the nocturnal FEV_1 trend[24]. It is likely that the bronchial obstruction (occurring during the night caused by the rise in the colinergic tone following the variation in the circadian rhythm) can produce a progressive worsening of the V/Q ratio with a consequent reduction in the nocturnal oxygenation. The tiotropium administering would contrast the progressive reduction in the airway flow with positive consequences on the nocturnal oxygenation. This effect wasn't observed after formoterol administering in our study. This drug produces a long-lasting bronchodilation and, probably, a long-lasting vasodilatation. This vasodilatation could contrast an improvement in the V/Q ratio. On the contrary, it is plausible that anticolinergics do not have any effects on the lung vessels[13], and therefore produce a poor effect on the V/Q ratio[17]. Some authors, have observed how M_3 receptor stimulation on the blood vessel wall could also produce a vasoconstriction[33]. The improvement in nocturnal oxygenation, after inhalation of Tiotropium, is responsible for a lower heart rate measured at night, as demonstrated by a negative significant relationship between Lowest SpO_2% and max heart rate. The reduction in heart rate, observed after Tiotropium, agrees with other studies that have observed the decrease in heart rate after anticholinergic therapy[18,32].

In conclusion, except for an initial transient hypoxemic effect, Formoterol does not seem to influence nocturnal hypoxemia in stable COPD patients. This is probably due to its effect on vasodilatation on the lung arterioles and therefore its negative influence on the V/Q ratio. Conversely, a single dose of tiotropium seems to decrease the severity in the nocturnal desaturations in stable COPD patients. This is due to its capability to contrast the nocturnal increase in the bronchial colinergic tone.

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