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Authors: Mario Cazzola, Pierachille Santus, Alice D'Adda, Silvia Pizzolato, Fabiano Di Marco, Stefano Centanni

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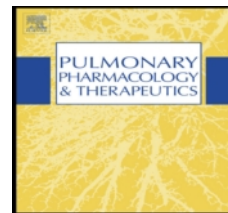
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# **Acute effects of higher than standard doses of salbutamol and ipratropium on tiotropium-induced bronchodilation in patients with stable COPD**

Mario Cazzola<sup>1</sup>, Pierachille Santus<sup>2</sup>, Alice D'Adda<sup>2</sup>, Silvia Pizzolato<sup>2</sup>, Fabiano Di Marco<sup>2</sup>, Stefano Centanni<sup>2</sup>

<sup>1</sup>Unit of Respiratory Diseases, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome, Italy, and <sup>2</sup>Unit of Respiratory Medicine, University of Milan, Ospedale San Paolo, Milan, Italy

Correspondence: Prof. Mario Cazzola, Dipartimento di Medicina Interna, Via Montpellier 1, 00133 Roma, Italy

## Abstract

Knowledge on the effects of the additive bronchodilatory effects of short-acting agents on the top of the effect of long-acting bronchodilators is limited. In this trial, we examined the influence of higher than conventional doses of the short-acting inhaled  $\beta$ 2-adrenergic agent salbutamol and the short-acting anticholinergic drug ipratropium bromide on bronchodilation induced by a regular treatment with the long-acting anticholinergic drug tiotropium 18  $\mu$ g/day in 30 patients with stable COPD. On 3 separate days, a dose-response curve to inhaled salbutamol (100  $\mu$ g puff<sup>-1</sup>), ipratropium bromide (20  $\mu$ g puff<sup>-1</sup>) or placebo was constructed 3 hours after inhalation of last dose of tiotropium, using one puff, one puff, two puffs and two puffs, for a total cumulative dose of 600  $\mu$ g salbutamol or 120  $\mu$ g ipratropium bromide. Doses were given at 30-min intervals and measurements made 15 min after each dose. At the highest cumulative dose, salbutamol showed a trend to be more effective than ipratropium bromide in improving FEV1 (0.157 L vs 0.125 L), and reducing sRaw (-4.52 kPa/s vs 3.57 kPa/s), although the differences between the two treatments were always not significant ( $p > 0.05$ ), whereas there was no substantial difference between the two drugs in changing FVC (0.179 L vs 0.168 L), IC (0.254 L vs 0.240 L), TGV (-0.444 L vs -0.441 L), TLC (-0.334 L vs -0.318 L) and RV (-0.467 L vs -0.498 L). Both drugs did not affect heart rate and SpO<sub>2</sub>. Our results indicate that there is not much difference in bronchodilation between adding higher than conventional doses of salbutamol or ipratropium bromide to tiotropium in patients with stable COPD. Effective improvement of the pulmonary function may be achieved in such a type of patients by adding salbutamol 600  $\mu$ g or ipratropium bromide 120  $\mu$ g to regular tiotropium. These is an interesting finding mainly for those COPD patients suffering from cardiovascular co-morbidities that are at highest risk of myocardial infarction, congestive heart failure, cardiac arrest and sudden cardiac death when treated with elevated doses of a  $\beta$ 2-agonist. (EudraCT number: 2007-001597-82)

## Introduction

National and international guidelines [1-3] suggest that long-acting bronchodilator therapy should always be considered when patients with COPD are symptomatic, but no distinction is made as to which class of drugs should be considered first, although anticholinergics agents are of noteworthy value since parasympathetic cholinergic pathways arising from the vagus nerve are implicated in the pathophysiology of airflow obstruction in COPD [4-6]. The most recently approved maintenance therapy for the treatment of stable COPD is the once-daily anticholinergic tiotropium. A systematic review has documented that this agent improves lung function, reduces lung hyperinflation, improves exercise endurance time, reduces COPD exacerbations and related hospitalisations, and improves quality of life and symptoms [7]. It has been suggested s likely that tiotropium might also influence the decline in forced expiratory volume in one second (FEV<sub>1</sub>), but a 4-year trial of tiotropium in COPD was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV<sub>1</sub> [8]. An additional benefit of tiotropium is a reduction in the need for relief medication to control breakthrough symptoms, although relief medication is still normally required on a daily basis in many COPD patients [9-12].

Short-acting inhaled bronchodilators ( $\beta_2$ -agonists and anticholinergics) are generally reserved for as required use because they bring quick relief for breathlessness. They can also be used to prevent or reduce symptoms that are known to be caused by specific situations such as exercise. It has been documented that the acute addition of a standard dose of ipratropium to long acting  $\beta_2$ -agonists, salmeterol [13] or formoterol [14] in their usual dosages, does not appear to improve pulmonary function, but higher than normal doses of an anticholinergic drug are able to induce further relief of bronchospasm in patients with COPD when an inhaled dose of a long-acting  $\beta_2$ -agonist is given first [15]. It has also been recognized that pre-treatment with a conventional dose of

a long-acting  $\beta_2$ -agonist does not preclude the possibility of inducing a further bronchodilation with higher than the customary dose of salbutamol in patients suffering from COPD [16].

In contrast, although there is good evidence that adding a normal dose of a long-acting  $\beta_2$ -agonist to tiotropium is effective [17, 18], data on the effects of the additive bronchodilatory effects of short-acting agents when a COPD patient is under regular treatment tiotropium are still largely lacking, although recently Kerstjens et al. [19] documented the additive bronchodilator effects in COPD of single conventional doses of a short-acting inhaled  $\beta_2$ -adrenergic (fenoterol 200  $\mu\text{g}$ ) and a short-acting anticholinergic drug (ipratropium 40  $\mu\text{g}$ ) when added to the once-daily, long-acting anticholinergic tiotropium. Ipratropium provided a small, but significant improvement in  $\text{FEV}_1$ , while no additional effect was observed in forced vital capacity (FVC). The most pronounced add-on effects in  $\text{FEV}_1$  and FVC were achieved with fenoterol.

This is interesting information, but in our opinion the real therapeutic potential of this addition can only be established using doses higher than those currently recommended in the marketing of these agents. We believe that when the response to bronchodilators is tested, a dose-response assessment should be undertaken, mainly in severe COPD. In fact, in patients classified as COPD, there is clearly a wide variation of response to bronchodilators and a surprising degree of reversibility can be achieved. Due to this variation in response, conventional drug doses may often be too small [20]. This is a crucial point when we are considering useful to add a short-acting bronchodilator as a rescue medication.

Therefore, we have examined the possible acute effects of higher than standard doses of a short-acting  $\beta_2$ -agonist, salbutamol, and a short-acting anticholinergic agent, ipratropium, on tiotropium-induced bronchodilation in patients with stable COPD.

## **Patients and Methods**

Thirty outpatients with moderate to severe COPD but in a stable phase of the disease were assessed. All were >50 years of age, current or former smokers (>10 pack years) without a history of asthmatic attacks, reporting chronic cough with or without sputum production and/or dyspnoea when walking quietly on level ground, or both; they had had no change in symptom severity or treatment in the preceding four weeks, had shown no signs of a respiratory tract infection in the month preceding or during the trial, had not been taking oral or inhaled corticosteroids for at least three months, and had a FEV<sub>1</sub> of <65% of predicted normal and a FVC of <70% after bronchodilators had been withheld for 24 hours and a best post-bronchodilator FEV<sub>1</sub>/FVC of less than 0.7. Studies have shown that many COPD patients have significant reversibility to bronchodilators [21] and that reversibility can either increase or decrease with time [22]. For these reasons we did not select patients according to any reversibility criteria. Patients with allergic rhinitis, atopy, positive skin test, or with a total blood eosinophil count over 400 mm<sup>-3</sup> were excluded. Patients were also excluded if they had any co-existing cardiovascular or lung disorder. Table 1 outlines the baseline characteristics of the population studied. The study, which was conducted according to the rules of the declaration of Helsinki at the San Paolo Hospital, Milan, Italy, was performed using a randomised, double blind, crossover design (EudraCT number: 2007-001597-82).

All patients, who were under regular treatment with tiotropium 18 µg/die from at least 6 months, received the daily dose of tiotropium. Functional testing was performed immediately before inhalation of treatment and after three hours. FEV<sub>1</sub>, inspiratory capacity (IC), and FVC were assessed. The patients were investigated in the morning in a sitting position. IC was determined by a slow manoeuvre (slow inspiration until maximum volume after regular tidal breathing), while functional residual capacity (FRC) was determined by asking patients to pant at a frequency of 51 Hz against a closed shutter. This manoeuvre was followed by a slow manoeuvre to obtain total lung capacity (TLC) and residual volume (RV). Specific airway resistance (sRaw) and thoracic gas volume (TGV)

were measured using a constant volume variable pressure body plethysmograph at each visit.

Three hours after the inhalation of tiotropium, a dose-response curve to inhaled salbutamol (100 µg/puff), ipratropium bromide (20 µg/puff) or placebo was constructed using one puff, one puff, two puffs, and two puffs - that is, a total cumulative dose of 600 µg salbutamol or 120 µg ipratropium bromide. Salbutamol, ipratropium bromide or placebo were administered from an MDI and holding chamber (AeroChamber) with a mouthpiece. Dose increments were given at 30 minute intervals with measurements being made 15 minutes after each dose. On three non-consecutive days all patients received one of the following: (1) 18 µg tiotropium + 600 µg salbutamol, (2) 18 µg tiotropium + 120 µg ipratropium bromide, or (3) 18 µg tiotropium + placebo.

The FEV<sub>1</sub> improvement induced by 600 µg salbutamol, 120 µg ipratropium or placebo (six puffs) over tiotropium was chosen as the primary outcome variable. With an estimation of the within subject variability (residual standard deviation) of 0.10 L, this crossover study with 30 patients had 80% power to detect a difference of at least 0.08 L between treatments. Analysis of spirometric data for each treatment was performed using the Student's *t* test for paired variables. Mean responses were also compared by multifactorial analysis of variance (ANOVA) to establish any significant overall effect between all treatments. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence limits (CI) was used to identify where differences were significant. A probability level of  $p < 0.05$  was considered significant for all tests.

## Results

All patients completed the three day study. There were no significant differences between the baseline spirometric values of the three treatment groups (FEV<sub>1</sub>,  $p =$



0.823). Moreover, tiotropium always induced a significant ( $p < 0.0001$ ) increase in all the explored parameters three hours after its inhalation (Table 2).

In the dose-response curve (figure 1) both salbutamol and ipratropium but not placebo elicited an evident increase in FEV<sub>1</sub>. Specifically, the further mean maximum increase induced by 600 µg salbutamol or 120 µg ipratropium (table 3) was 0.157 L (95% CI of differences 0.108 to 0.206) and 0.125 L (95% CI of differences 0.068 to 0.182), respectively, whereas that elicited by placebo was 0.044 L (95% CI of differences 0.006 to 0.082). Maximum values of bronchodilation induced by 600 µg salbutamol or 120 µg ipratropium were statistically different ( $p < 0.0001$ ) from their pre-inhalational values (table 3). The mean difference between FEV<sub>1</sub> after tiotropium + 600 µg salbutamol and that after tiotropium + placebo (six puffs) showed a mean difference of 0.081 L (95% CI of differences 0.027 to 0.136) that was statistically significant ( $p = 0.0048$ ). Also the mean difference between FEV<sub>1</sub> after tiotropium + 120 µg ipratropium and that after tiotropium + placebo (six puffs) (0.068 L; 95% CI of differences 0.003 to 0.132) was statistically significant ( $p = 0.0404$ ), whereas that between FEV<sub>1</sub> after tiotropium + 600 µg salbutamol and that after tiotropium + 120 µg ipratropium was not statistically significant ( $p > 0.05$ ).

Changes in sRaw, FVC, IC, TGV, TLC and RV dose-response curves are shown in figure 1 and 2. At the highest cumulative dose, salbutamol was more effective than ipratropium bromide in reducing sRaw (-4.52 kPa/s vs 3.57 kPa/s), although the difference between the two treatments was not significant ( $p > 0.05$ ), whereas there was no substantial difference between the two drugs in changing FVC (0.179 L vs 0.168 L), IC (0.254 L vs 0.240 L), TGV (-0.444 L vs -0.441 L), TLC (-0.334 L vs -0.318 L) and RV (-0.467 L vs -0.498 L) (table 2).

All drugs did not affect heart rate and SpO<sub>2</sub> (Table 2 and 3). Moreover, no patient complained of adverse symptoms, such as dry mouth and noted tremor, or reported any difference in the taste of the inhalers.

## Discussion

Our study shows that a regular treatment with tiotropium does not reduce the possibility of inducing a further bronchodilation with the addition a short acting bronchodilator in patients who are suffering from COPD. The documentation that even in patients suffering from stable COPD under regular treatment with tiotropium there is the possibility of further improvement in lung function clearly indicates that such a type of treatment does not elicit the maximal bronchodilation. This is not a surprise because usually bronchodilators are not used at maximal dosage in order to avoid the possible side effects [23]. On the contrary, what is noteworthy is the documentation the there is not substantial difference in adding a short acting  $\beta$ -agonist or a short acting anticholinergic agent. This finding indicates that it is not necessary to choose a second bronchodilator with different mechanisms of action when we wish to induce an improvement in bronchodilation. It is an important message mainly for those COPD patients suffering from cardiovascular co-morbidities. In fact, higher than customary doses of a  $\beta$ 2-agonist are associated with an increased risk of myocardial infarction, congestive heart failure, cardiac arrest and sudden cardiac death [24]. The degree of risk appears to be dose-dependent, and may be highest for new users and those with concomitant cardiac conditions [25].

We must highlight that in this study we have chosen a cumulative dose of 120  $\mu$ g ipratropium and 600  $\mu$ g salbutamol. It has been documented that FEV<sub>1</sub> and FVC reached a plateau after administration of a cumulative dose of 280  $\mu$ g of ipratropium bromide [26], and higher doses (up to 4 mg) of inhaled albuterol have been shown to cause slightly more bronchodilatation than standard doses from a metered-dose inhaler in patients with severe chronic airflow limitation [27]. However, it is well known that although maximal bronchodilation can be achieved with a high dose of a single agent, combining two bronchodilators allows the use of lower doses, with the same efficacy results and fewer adverse effects [23]. For example, it has been reported that in terms of improvement in FEV<sub>1</sub>, one puff of

ipratropium and fenoterol 100/40 equalled two puffs of fenoterol (200 µg) and four puffs of ipratropium (160 µg) [28]. It must be highlighted that all patients in this study were under regular treatment with tiotropium.

To our best knowledge, only three other studies have examined the combination of a long-acting anticholinergic plus a short-acting  $\beta_2$ -agonist. Apart from the above mentioned study of Kerstjens et al. [19], we must quote that in a study of 11 patients with COPD, the bronchodilating effect of glycopyrrolate was about equal to that of metaproterenol but lasted longer (8 h versus 5 h) [29] whereas the effect of glycopyrrolate and metaproterenol was greater than that of monotherapy (the mean peak percentage improvement in FEV<sub>1</sub> over baseline was 35% for the combination versus 25% for either drug alone). Another study had documented that the addition of a single treatment with aerosolized glycopyrrolate to hourly treatments with salbutamol produces a greater percent improvement in FEV<sub>1</sub> than does salbutamol alone in the treatment of patients with COPD exacerbation (56% versus 19% improvement in FEV<sub>1</sub> from pre-treatment value,  $p = .008$ ) [30].

Our results fit well with the documentation that add-on therapy of the long-acting  $\beta_2$ -agonist formoterol to tiotropium maintenance therapy significantly improved spirometric variables, including IC [18]. We cannot exclude that the larger bronchodilatory response that we observed when a short-acting bronchodilator was given after tiotropium should be justified by a carry over effect, considering that tiotropium is a long-lasting bronchodilator. Nonetheless, it is well known that the mean peak bronchodilation with tiotropium in COPD patients is reached after 3 h [31], and in the present study we have documented that the administration of a second bronchodilator added 3 h after the inhalation of tiotropium could amplify its maximum bronchodilation. This finding seems to be important because it indicates the possibility that a patient who is under regular tiotropium and is unable to perceive bronchodilation or must perform an exercise could use a high dose of a short-acting bronchodilator as reliever medication when needed.

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**Table 1** - Anthropometric data and pulmonary function of patients

Patient	Sex	Age (years)	Smoker (pack/year)	FEV <sub>1</sub> (% predicted)	FVC (% predicted)
1	M	77	EX (90)	59.2	77.2
2	M	73	EX (30)	44.5	60.7
3	F	71	Y (35)	64.9	85.7
4	M	59	EX (35)	44.3	58.8
5	M	76	EX (100)	49.8	71.2
6	M	60	EX (30)	55.4	86.4
7	F	74	Y (25)	55.6	91.6
8	M	73	EX (40)	51.0	72.0
9	M	71	EX (50)	37.5	69.4
10	M	74	EX (50)	44.9	76.2
11	M	69	EX (40)	63.9	90.9
12	M	68	Y (45)	45.3	74.3
13	M	78	EX (50)	50.2	71.2
14	M	75	EX (30)	50.4	65.7
15	M	50	EX (45)	30.9	68.7
16	M	74	EX (50)	43.1	65.7
17	F	58	Y (50)	40.4	72.3
18	M	69	Y (55)	44.6	90.0
19	F	66	EX (35)	61.0	77.2
20	F	70	EX (40)	52.8	62.1
21	M	76	EX (60)	37.6	65.1
22	M	59	Y (40)	49.4	77.0
23	F	60	EX (50)	52.0	81.4
24	M	61	Y (40)	54.9	72.4
25	M	71	Y (50)	47.1	79.2
26	M	74	EX (50)	61.6	87.0
27	M	74	Y (30)	44.5	70.2
28	M	74	EX (60)	64.6	78.3
29	M	73	Y (50)	40.7	58.0
30	M	66	Y (120)	63.3	75.0



**Table 2** - Baseline values and changes in the examined parameters 3h after tiotropium

	Placebo arm	Salbutamol arm	Ipratropium bromide arm
FEV <sub>1</sub> , L Baseline 3h after tiotropium	1.350, 1.222 to 1.477 0.238, 0.164 to 0.311***	1.341, 1.208 to 1.473 0.253, 0.150 to 0.281***	1.330, 1.185 to 1.475 0.244, 0.166 to 0.322***
sRaw, kPa/s Baseline 3h after tiotropium	18.78, 13.96 to 23.60 -8.33, -11.76 to - 4.89***	17.77, 14.30 to 21.25 -7.59, -10.03 to 5.15***	18.86, 13.91 to 23.80 -8.21, -11.92 to - 4.50***
FVC, L Baseline 3h after tiotropium	2.499, 2.285 to 2.712 0.409, 0.293 to 0.525***	2.492, 2.248 to 2.736 0.408, 0.259 to 0.557***	2.441, 2.219 to 2.662 0.441, 0.294 to 0.588***
IC, L Baseline 3h after tiotropium	2.033, 1.817 to 2.250 0.235, 0.106 to 0.364***	1.975, 1.732 to 2.219 0.309, 0.185 to 0.433***	2.040, 1.778 to 2.302 0.247, 0.126 to 0.368***
TGV, L Baseline 3h after tiotropium	5.269, 4.907 to 5.631 -0.525, -0.758 to - 0.292***	5.182, 4.845 to 5.519 -0.370, -0.635 to - 0.104**	5.164, 4.748 to 5.581 -0.400, -0.613 to - 0.187***
TLC, L Baseline 3h after tiotropium	7.373, 6.902 to 7.843 -0.489, -0.765 to - 0.213**	7.234, 6.778 to 7.691 -0.302, -0.463 to - 0.142***	7.180, 6.697 to 7.663 -0.277, -0.485 to - 0.069*
RV, L Baseline 3h after tiotropium	4.335, 3.866 to 4.803 -0.823, -1.128 to 0.518***	4.154, 3.766 to 4.543 -0.539, -0.728 to - 0.351***	4.132, 3.674 to 4.590 -0.483, -0.668 to - 0.298***
spO <sub>2</sub> , % Baseline 3h after tiotropium	95.73, 95.24 to 96.22 -0.53, -0.95 to -0.12*	95.60, 95.10 to 96.10 -0.03, -0.42 to 0.35	95.40, 94.80 to 96.00 -0.10, -0.61 to 0.41
Heart rate, beats/min Baseline 3h after tiotropium	78.10, 75.06 to 81.14 -2.20, -4.84 to 0.44	77.13, 73.61 to 80.66 -1.60, -3.89 to 0.69	75.07, 71.97 to 78.16 0.00, -2.90 to 2.90

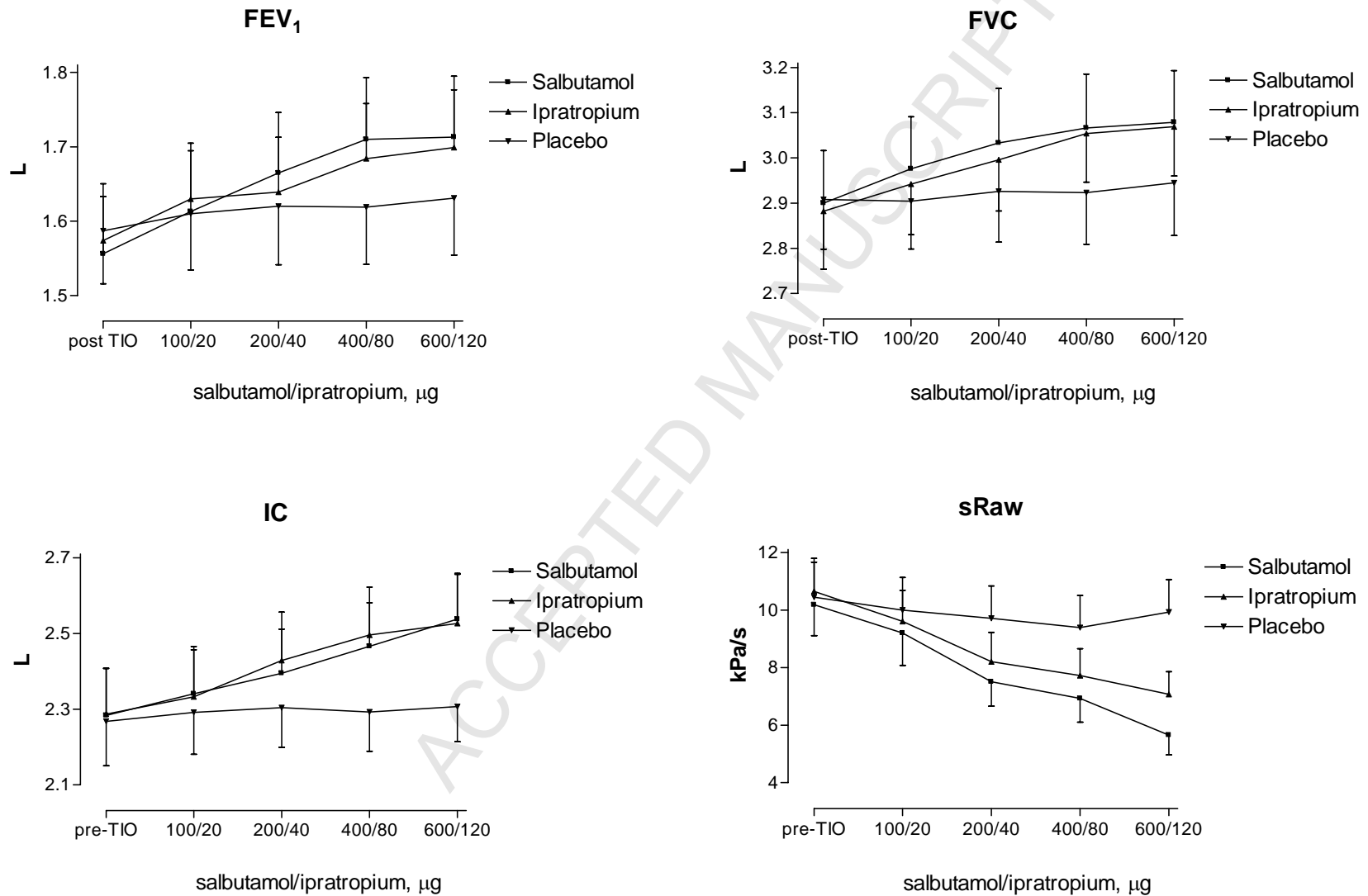
Values are mean (95% confidence interval). \*p< 0.05, \*\*p< 0.01 and \*\*\*p<0.001 vs. baseline values.

**Table 3** - Changes in the examined parameters at the highest cumulative dose of salbutamol (600 µg), ipratropium (120 µg) and placebo (6 puffs) when compared with the pre-inhalational values.

	Placebo	Salbutamol	Ipratropium bromide
FEV <sub>1</sub> , L	0.044, 0.006 to 0.082	0.157, 0.108 to 0.206***	0.125, 0.068 to 0.182***
sRaw, kPa/s	-0.52, -1.23 to 0.09	-4.52, -6.12 to -2.93***	-3.57, -5.02 to -2.13***
FVC, L	0.037, -0.028 to 0.102	0.179, 0.101 to 0.258***	0.168, 0.053 to 0.282**
IC, L	0.038, -0.069 to 0.145	0.254, 0.128 to 0.379***	0.240, 0.099 to 0.381**
TGV, L	-0.129, -0.265 to 0.008	-0.444, -0.163 to -0.726**	-0.441, -0.220 to 0.661***
TLC, L	-0.102, -0.205 to 0.001	-0.334, -0.169 to -0.518***	-0.318, -0.164 to -0.471***
RV, L	-0.112, -0.228 to 0.004	-0.467, -0.678 to -0.257***	-0.498, -0.687 to -0.309***
spO <sub>2</sub> , %	0.33, -0.22 to 0.88	-0.07, -0.69 to 0.56	0.50, -0.06 to 1.06
Heart rate, beats/min	-0.27, -2.19 to 1.66	0.63, -2.54 to 3.81	-0.10, -2.49 to 2.29

Values are mean (95% confidence interval).\*\*p< 0.01 and \*\*\*p<0.001 vs. pre-inhalational values.

**Figure 1** – Mean dose-response curves to inhaled salbutamol, ipratropium bromide, or placebo construction 3 h after inhaling tiotropium (18 µg) for FEV<sub>1</sub>, FVC, IC and sRaw. Values are mean ± SE.



**Figure 2** – Mean dose-response curves to inhaled salbutamol, ipratropium bromide, or placebo construction 3 h after inhaling tiotropium (18 µg) for TGV, TLC and RV. Values are mean ± SE.

