

Dose-response curve to salbutamol during acute and chronic treatment with formoterol in COPD

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Background: Use of short-acting β_2 -agonists in chronic obstructive pulmonary disease (COPD) during treatment with long-acting β_2 -agonists is recommended as needed, but its effectiveness is unclear. The purpose of this study was to assess the additional bronchodilating effect of increasing doses of salbutamol during acute and chronic treatment with formoterol in patients with COPD.

Methods: Ten patients with COPD underwent a dose-response curve to salbutamol (until 800 μg of cumulative dose) after a 1-week washout (baseline), 8 hours after the first administration of formoterol 12 μg (day 1), and after a 12-week and 24-week period of treatment with formoterol (12 μg twice daily by dry powder inhaler). Peak expiratory flow, forced expiratory volume in one second (FEV_1), forced vital capacity, and inspiratory capacity were measured at the different periods of treatment and at different steps of the dose-response curve.

Results: Despite acute or chronic administration of formoterol, maximal values of peak expiratory flow, FEV_1 , and forced vital capacity after 800 μg of salbutamol were unchanged compared with baseline. The baseline FEV_1 dose-response curve was steeper than that at day 1, week 12, or week 24 ($P < 0.0001$). Within each dose-response curve, FEV_1 was different only at baseline and at day 1 ($P < 0.001$), when FEV_1 was still greater at 800 μg than at 0 μg ($P < 0.02$). In contrast, the forced vital capacity dose-response curves were similar at the different periods, while within each dose-response curve, forced vital capacity was different in all instances ($P < 0.001$), always being higher at 800 μg than at 0 μg ($P < 0.05$).

Conclusion: In patients with stable COPD, the maximal effect of salbutamol on peak expiratory flow, FEV_1 , and forced vital capacity was unchanged after either acute or chronic treatment with formoterol. With increasing doses of salbutamol, FEV_1 increased only after acute administration of formoterol. Forced vital capacity also significantly improved during long-term treatment with formoterol.

Keywords: chronic obstructive pulmonary disease, salbutamol, formoterol, long-acting β_2 -agonists

Introduction

The effect of increasing doses of short-acting β_2 -agonists (SABA) in patients with stable COPD during long-term treatment with long-acting β_2 -agonists (LABA) is presently unknown. The current guidelines recommend treating COPD patients with bronchodilating drugs,¹ and among them, LABA are widely used.²⁻⁴ Indeed, although changes in forced expiratory volume in one second (FEV_1) after acute or chronic administration of bronchodilating agents are usually scarce in COPD, other volume parameters, such as inspiratory capacity and forced vital capacity, must be taken into account to assess the effectiveness of therapy with bronchodilators in these patients.⁵ During regular LABA

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treatment, if the airflow obstruction increases abruptly, a therapeutic option is to add SABA as rescue medication, trying to achieve rapid and effective control of airway obstruction and related symptoms. However, regular treatment with LABA could reduce the bronchodilatory response to repeated doses of SABA because of occupation or potential downregulation of β_2 adrenoreceptors.⁶ Cazzola et al performed a placebo-controlled study of the effect of acute pretreatment with LABA (salmeterol, formoterol, or oxitropium via metered dose inhaler) on the bronchodilating response to incremental doses of inhaled salbutamol in a cohort of patients with COPD and marked reversibility of airway obstruction, as assessed by acute FEV₁ change.⁷ All long-acting bronchodilators elicited a significant increase in FEV₁, and a significant dose-dependent increment in FEV₁ was seen after salbutamol administration, suggesting that salbutamol is useful as a “rescue agent” in COPD when using long-acting bronchodilators, including LABA.⁷ However, this study did not address the relevant clinical question of whether or not similar results would be obtained after long-term use of LABA in patients with COPD.⁸ Therefore, the aim of the present study was to assess if the main indices of airway obstruction are positively affected in the dose-response curve to inhaled salbutamol not only after acute but also after chronic treatment with formoterol, a long-acting pure β_2 -agonist, in patients with stable COPD.

Methods

Approval of our ethics committee was obtained prior to embarking on this research. After providing their written informed consent, 15 consecutive patients were enrolled, suffering from COPD with moderate-to-severe airway obstruction, defined according to the following criteria: smoking history of more than 20 pack-years and/or presence of other known risk factors for COPD (frequent respiratory tract infections in childhood, chronic cough and phlegm, occupational exposures, indoor pollutants by biomass fuel, α 1-antitrypsin deficiency); baseline FEV₁/vital capacity ratio < 5th percentile of lower limit of normal, corresponding to a FEV₁/vital capacity ratio < 88% predicted^{9,10} and a baseline FEV₁ < 80% predicted and >30% predicted; increase of FEV₁ < 10% of predicted and 200 mL after 400 μ g of inhaled salbutamol;^{9,10} absence of history of bronchial asthma, allergic rhinitis or atopy; and no concomitant restrictive lung or chest wall disorders. To be eligible for the study, patients had to be in a stable condition without any symptoms or treatment changes in the 4 weeks prior to the study, have had no exacerbations in the preceding 12 weeks, and be able to perform forced expiratory maneuvers adequately. No patient was

suffering from known cardiovascular disease, a neuromuscular disorder, or any metabolic or hormonal alterations. All patients treated with inhaled corticosteroids had to stop these drugs at least 4 weeks before the beginning of the study. No other concomitant drugs were allowed during the study, except for SABA as rescue medication. On the first day, patients were asked to withdraw any LABA for one week and SABA for 12 hours before starting the study.

After the washout period, each patient performed spirometry with a maximal flow/volume curve, underwent measurement of DLCO (diffusing capacity of the lung for carbon monoxide) and lung volumes by the multibreath helium dilution method, and assessment of tidal expiratory flow limitation with the negative expiratory pressure technique.¹¹ Afterwards, they underwent a dose-response curve to salbutamol, performing a series of spirometric maneuvers with maximal expiratory flow/volume curve 20 minutes after inhalation (metered dose inhaler + spacer) of subsequent doses of salbutamol (0 μ g, 100 μ g, 100 μ g, 200 μ g, 400 μ g), reaching a cumulative dose of 800 μ g at baseline period. Treatment with formoterol dry powder inhaler 12 μ g twice daily was then prescribed, starting from the following morning with no other inhaled drug. In all patients, the dose-response curve to salbutamol as previously described was repeated on the first day of treatment, and after 12 weeks and 24 weeks. These tests were always performed eight hours after the morning dose of formoterol. The maximal cumulative dose of salbutamol of 800 μ g was chosen to avoid the potentially dangerous effects of acute β_2 stimulation on cardiac function elicited by higher doses of the drug and because it is highly improbable that patients with COPD would use more than eight puffs of salbutamol as a single rescue dose in real life. On each occasion, inspiratory capacity was measured prior to the maximal expiratory flow-volume curve by inspiring from end expiratory lung volume to total lung capacity. The predicted inspiratory capacity values were those proposed by Tantucci et al.¹²

Adherence to treatment with formoterol was assessed at each period by checking the dose counter of the dry powder inhaler. Monitoring of side effects was performed by evaluating heart rate and blood pressure values before and after each dose of salbutamol.

Spirometry

A computerized water-sealed light-bell Stead-Wells spirometer (Biomedin, Padua, Italy) was used and the operator was assisted during the test with software able to verify both acceptability and repeatability of spirometric maneuvers online.

All measurements were made in accordance with the guidelines of the American Thoracic Society,^{9,10} with the subjects in the sitting position, wearing a nose clip. During the study, the neck was held in a fixed neutral position to avoid changes associated with different neck positions, and no inspiratory pause was allowed at total lung capacity before performing the forced expiratory maneuver. We adopted the reference values for pulmonary function parameters proposed by Quanjer et al.¹³

Negative expiratory pressure test

The patients breathed quietly, wearing a nose clip, through a mouthpiece and a heated pneumotachograph (Series 3700; Hans Rudolph, Kansas City, MO) connected to a differential pressure transducer (Raytech DP55 ± 3 cm H₂O; Raytech Instruments, Vancouver, Canada) to measure flow. Pressure was measured at the mouth by a differential pressure transducer (Raytech DP55 ± 100 cm H₂O). The pneumotachograph was assembled in series with a Venturi device that created a negative pressure in the circuit which could be precisely fixed. This technique is described fully elsewhere.^{5,11}

Statistical analysis

The sample size of 15 provided a statistical power of 90% ($\beta = 0.10$) to detect the smallest clinically relevant mean difference of 140 mL of FEV₁¹⁴ with a standard deviation of the differences in response to bronchodilators of 140 mL of FEV₁ found in our laboratory at 5% of significance level ($\beta = 0.05$) for a paired *t*-test. Average data of the variables of interest were compared by multifactorial analysis of variance to establish any significant overall effect among the four periods. If significant, Sheffé multiple range test was used to identify

which differences were significant. Analysis of variance for repeated measures with the Bonferroni correction was performed to analyze and compare data within the dose-response curve of each period (baseline, day 1, week 12, week 24). A *P* value < 0.05 was considered to be statistically significant. Data are expressed as means ± standard deviation. Statistical analysis was performed using the Stat View software package (Stat View; SAS Institute Inc, Cary, NC).

Results

Five of the 15 patients dropped out (four because of noncompliance with LABA and one because of an exacerbation at week 10), and 10 (including seven males) successfully completed the study. Anthropometric and functional data are shown in Table 1. Three patients were flow-limited at rest during tidal expiration in the sitting position with an inspiratory capacity of 56.6% ± 12.0% predicted, while seven patients were not flow-limited and had a normal inspiratory capacity of 94.0% ± 7.8% predicted. All patients were former smokers (range 20–54 pack-years). All patients had quit smoking at least 1 year before enrolling in this study and no patient smoked before the pulmonary function test. No changes in smoking habit were observed and no exacerbation was reported among patients who completed the protocol.

Mean values for FEV₁, forced vital capacity, peak expiratory flow, FEV₁/forced vital capacity, and inspiratory capacity, and the response to subsequent cumulative doses of salbutamol at baseline, day 1, week 12, and week 24 periods are shown in Table 2. The FEV₁ and forced vital capacity dose-response curves to salbutamol at the different periods are shown in Figure 1.

Table 1 Anthropometric and functional data of patients who were enrolled (n = 15) and who completed the study (n = 10)

	(n = 15)		(n = 10)	
Gender (M/F)	11M/4F		7M/3F	
Age (yrs)	63.4 ± 10.6		61.7 ± 10.4	
Body weight (kg)	69.5 ± 13.0		70.5 ± 12.2	
Height (m)	1.63 ± 0.1		1.62 ± 0.1	
BMI (kg/m ²)	26.1 ± 4.0		26.7 ± 4.0	
	Absolute values	(% predicted)	Absolute values	(% predicted)
FEV ₁ /VC	43.7% ± 11.1%	57.5 ± 15.2	40.9% ± 11.0%	53.5 ± 14.7
FEV ₁	1.36 ± 0.51 L	53.3 ± 16.5	1.29 ± 0.53 L	50.4 ± 16.9
FVC	2.66 ± 0.69 L	83.4 ± 16.1	2.62 ± 0.81 L	82.5 ± 19.6
IC	2.29 ± 0.70 L	81.8 ± 12.6	2.24 ± 0.78 L	82.8 ± 20.2
TLC	5.49 ± 0.93 L	98.8 ± 17.9	5.76 ± 0.95 L	104.4 ± 15.8
FRC	3.24 ± 0.71 L	103.5 ± 23.2	3.42 ± 0.75 L	109.4 ± 25.8
RV	2.46 ± 0.62 L	115.7 ± 34.6	2.59 ± 0.66 L	123.7 ± 33.5
DLCO	12.24 ± 4.93 mL/min*mmHg	53.2 ± 20.9	12.8 ± 5.32 mL/min*mmHg	54.9 ± 22.9

Note: Data are mean ± standard deviation.

Abbreviations: BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; VC, vital capacity; RV, residual volume.

Table 2 Lung function parameters at baseline and at each period of treatment with formoterol for each cumulative dose of salbutamol

Period		0 µg	100 µg	200 µg	400 µg	800 µg
Baseline	FEV ₁	50.4 ± 16.9	52.2 ± 16.2	54.4 ± 17.1	55.8 ± 16.2	58.2 ± 16.8*
	FVC	82.5 ± 19.6	85.3 ± 18.8	88.2 ± 17.1	90.3 ± 16.93	92.3 ± 14.6*
	PEF	55.6 ± 13.3	56.9 ± 11.2	58.8 ± 11.7	59.7 ± 13.1	60.0 ± 13.4*
	FEV ₁ /FVC (%)	48.6 ± 9.2	48.8 ± 8.3	50.4 ± 9.2	50.4 ± 7.9	50.9 ± 9.4
	IC	82.8 ± 20.2	85.3 ± 18.8	88.2 ± 17.1	90.3 ± 16.9	91.3 ± 14.6
	IC (3 FL pts)	56.6 ± 12.8	57.8 ± 13.4	61.6 ± 9.3	63.6 ± 13.7	67.4 ± 13.1
Day 1 [§]	FEV ₁	55.2 ± 16.8	56.5 ± 15.9	58.1 ± 15.4	58.3 ± 15.4	58.7 ± 14.6*
	FVC	86.2 ± 20.7	88.8 ± 19.2	91.5 ± 19.6	92.1 ± 18.4	92.7 ± 18.6*
	PEF	59.1 ± 14.9	60.5 ± 14.6	61.4 ± 13.8	60.8 ± 14.3	62.2 ± 12.4
	FEV ₁ /FVC (%)	51.2 ± 7.7	50.9 ± 7.5	50.7 ± 7.8	52 ± 9.9	51.9 ± 9.0
	IC	86.2 ± 20.7	88.8 ± 19.2	91.5 ± 19.7	92.1 ± 18.4	91.7 ± 18.7
	IC (3 FL pts)	58.9 ± 10.3	64.4 ± 8.2	65.8 ± 6.7	66.5 ± 8.6	67.5 ± 7.2
Week 12 [§]	FEV ₁	54.1 ± 17.6	54.5 ± 17.0	56.4 ± 15.7	56.4 ± 15.7	57.5 ± 16.4
	FVC	85.2 ± 18.3	86.4 ± 18	87.2 ± 15.8	87.7 ± 15.7	90.0 ± 14.8*
	PEF	58.1 ± 15.3	60 ± 12.8	57.3 ± 13.7	57.7 ± 13.7	59.9 ± 15.3
	FEV ₁ /FVC (%)	50.2 ± 8.1	50.4 ± 8.9	51.7 ± 8.0	51.1 ± 7.9	50.5 ± 8.5
	IC	86.0 ± 18.9	86.9 ± 18.6	89.0 ± 18.2	89.8 ± 16.9	91.0 ± 19.3
	IC (3 FL pts)	58.3 ± 13.0	60.7 ± 14.9	63.7 ± 14.9	64.6 ± 10.9	65.2 ± 9.9
Week 24 [§]	FEV ₁	55.3 ± 18.6	56.3 ± 18.8	57.3 ± 18.2	57.3 ± 18.2	58.1 ± 18.7
	FVC	88.1 ± 19.9	88.5 ± 20.9	90.3 ± 20.3	90.7 ± 20.8	92.5 ± 20.3*
	PEF	57.5 ± 16.1	58.2 ± 17.3	58.1 ± 15.6	60.4 ± 17.4	60.6 ± 16.6
	FEV ₁ /FVC (%)	50.6 ± 8.3	50.6 ± 8.2	51.3 ± 8.1	50.7 ± 7.9	50.3 ± 8.3
	IC	88.1 ± 19.5	88.5 ± 20.7	90.3 ± 20.7	90.7 ± 20.8	92.5 ± 20.4
	IC (3 FL pts)	56.4 ± 9.2	57.8 ± 11.7	60.8 ± 12.4	64.9 ± 12.9	64.7 ± 12.9

Notes: Data are mean ± standard deviation and expressed as % predicted, except for FEV₁/FVC ratio. **P* < 0.05 versus 0 µg; [§]*P* < 0.001 versus baseline for FEV₁. **Abbreviations:** BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; VC, vital capacity; ICFL, flow limited at rest.

Following both acute and chronic administration of formoterol, FEV₁ before salbutamol (0 µg) was always higher when compared with baseline (day 1, week 12 and week 24 versus baseline, *P* < 0.01, Figure 1 and Table 2).

At the different assessment periods, the dose-response curves were different for FEV₁ (*P* < 0.01), and almost significantly different for peak expiratory flow (*P* = 0.056), but this was not the case for forced vital capacity. In particular, the FEV₁ dose-response curve at baseline was significantly steeper than those at day 1, week 12, and week 24 (*P* < 0.0001, Figure 1).

Within each dose-response curve for salbutamol, FEV₁ values were significantly different only at baseline and day 1 (*P* < 0.001) and peak expiratory flow values only at baseline (*P* < 0.001), while forced vital capacity values remained significantly different at all periods of the study (*P* < 0.001). In particular, FEV₁ increased significantly between dose 0 µg and dose 800 µg of salbutamol both at baseline and at day 1 (*P* < 0.05), and peak expiratory flow only at baseline (*P* < 0.01). In contrast, forced vital capacity increased from dose 0 µg to dose 800 µg of salbutamol in all instances (*P* < 0.05, Table 2).

At each period of the study, the inspiratory capacity values showed no significant changes during incremental doses of salbutamol when all patients were included. This occurred because inspiratory capacity was normal and remained unchanged after bronchodilators in seven patients who were not flow-limited. However, if only three tidally flow-limited COPD patients were taken into account, a trend similar to that found for forced vital capacity was observed also for inspiratory capacity (Table 2).

Discussion

The main results of the study were: the maximal effect after the last dose of salbutamol on peak expiratory flow, FEV₁, and forced vital capacity did not change compared with baseline at each period of treatment with formoterol; while the significant FEV₁ increment occurring after salbutamol on top of the first dose of formoterol was lost during chronic treatment, a significant improvement in forced vital capacity was still observed during long-term treatment with formoterol, although always at the highest dose of salbutamol (800 µg); and no changes in inspiratory capacity were found in any patient, but at least in those with baseline tidal

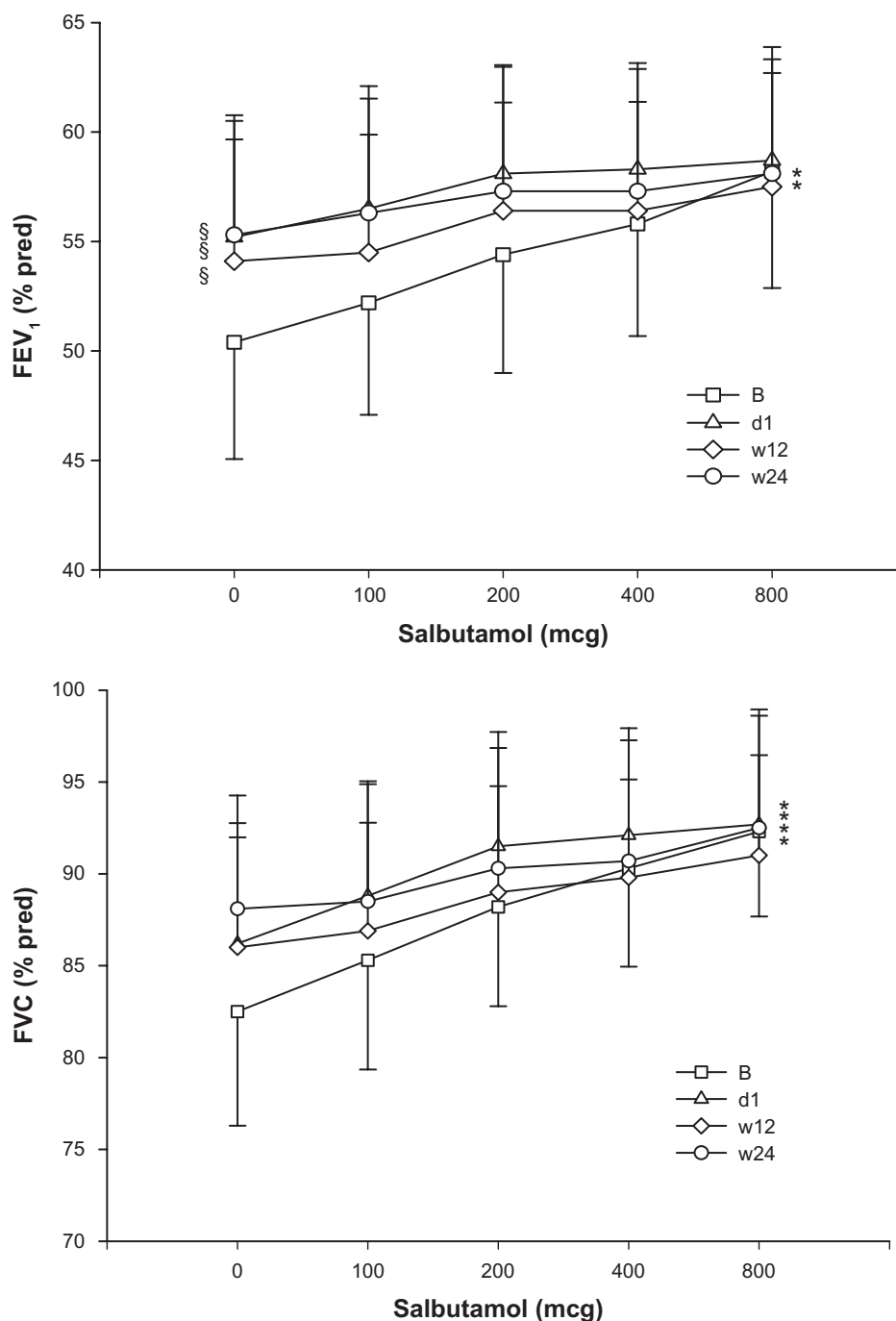


Figure 1 FEV₁ and FVC are shown as % predicted at baseline and at each period of treatment for each cumulative dose of salbutamol.

Notes: * $P < 0.05$ versus 0 μg for FEV₁ at 800 μg at baseline and day 1, and for FVC at 800 μg at all periods; [§] $P < 0.001$ versus baseline; symbols are means, bars are standard error of the mean.

Abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

expiratory flow limitation and resting dynamic hyperinflation, changes similar to forced vital capacity were observed also for inspiratory capacity.

Our goal was to assess the bronchodilating effect elicited by acute SABA administration in patients with stable moderate-to-severe COPD during short-term and long-term treatment with LABA. Formoterol is a full LABA with a

very rapid onset of bronchodilating action that lasts for about 12 hours due to its lipophilic properties.¹⁵ In COPD, prolonged administration of formoterol at a dosage of 12 μg twice daily is associated with better FEV₁ and peak expiratory flow values over time and significant improvement of clinical outcomes.¹⁶ However, the aim of this study was to measure functional changes and not clinical improvement.

Inhaled SABA that induce bronchodilation in a few minutes and reach maximal effect after 20–30 minutes are usually the preferred rescue bronchodilators for the treatment of either intermittent or worsening symptoms in patients with COPD. Clinical studies that have evaluated the effect of SABA during long-term treatment with LABA in patients with COPD are lacking.

Previously, the effect of doubling doses of salbutamol (until a cumulative dose of 800 μg) given two hours after acute administration of different long-acting bronchodilators, such as formoterol, salmeterol, and oxitropium, was investigated in patients with COPD characterized by marked acute reversibility of airflow obstruction.⁷ In these circumstances, the maximal bronchodilating effect obtained at the highest dose of salbutamol was unchanged after a single dose of both LABA and oxitropium, as compared with baseline. However, both FEV₁ and forced vital capacity showed a significant increase with administration of salbutamol following acute pretreatment with either LABA or oxitropium.

In the present study, these results were confirmed at least for formoterol also after eight hours, although to a lesser extent due to the half dose of the drug (12 μg versus 24 μg) and mainly due to the different phenotype of our COPD patients who had no significant reversibility of their airflow obstruction after acute inhalation of 400 μg of salbutamol.

On the other hand, during chronic treatment with formoterol, further improvements of FEV₁ and peak expiratory flow following administration of salbutamol were scarce and not significant either at 12 or 24 weeks of therapy, at least eight hours after LABA administration (Figure 1 and Table 2).

In contrast, the forced vital capacity increment after the highest cumulative dose of salbutamol was greater and still significant at 12 weeks and 24 weeks of therapy with formoterol. The aim of the study was to measure functional changes and not clinical improvement, and a similar trend was observed for inspiratory capacity in three tidally flow-limited and dynamically hyperinflated COPD patients at rest (Table 2).

Some speculation can be made regarding these findings. It is well known that peak expiratory flow and FEV₁ changes are sensitive to a decrease in airflow resistance, mainly in the large and medium caliber airways, while the forced vital capacity changes reflect a diminution of air trapping (ie, plethysmographic residual volume) because of reduction of airflow resistance in the small airways and their closure at lower lung volumes.¹⁷ It is conceivable that formoterol inhaled as a dry powder may reach the central airways and rapidly saturate the β_2 receptors located in these airways. Therefore, after a few weeks of treatment with formoterol, the additional

bronchodilating effect of salbutamol, as reflected by the peak expiratory flow and FEV₁ changes, may be mild even at high doses. Conversely, the dry powder formulation of formoterol might have more difficulty in reaching the peripheral airways and occupy all β_2 receptors,¹⁸ leaving salbutamol given by metered dose inhaler as a possible means of further dilating and/or reopening these airways.

Such a possibility could be enhanced by the fact that even if β_2 adrenoreceptors are widely distributed in the bronchial tree, and their number increases in airway smooth muscle with increasing airway generation, showing higher density in smaller than in larger airways.^{19,20}

Thus, the opportunity of further stimulating β_2 receptors in the peripheral airway smooth muscle cells may allow high doses of salbutamol inhaled by metered dose inhaler to substantially increase forced vital capacity (and decrease air trapping) by reducing expiratory airflow resistance at low lung volumes, even after many weeks of treatment with formoterol (Figure 1). Such reasoning may also explain the inspiratory capacity changes observed in three of our COPD patients, in whom baseline inspiratory capacity was markedly reduced because of dynamic pulmonary hyperinflation due to resting tidal expiratory flow limitation.⁵

The choice of focusing the effect on lung function following increasing doses of salbutamol on top of regular treatment with formoterol eight hours after its morning dose was based on the widely recognized fact that the bronchodilating effect of a pure β_2 agonist such as formoterol (when given alone) tends to decline after 8 hours (especially during chronic treatment). Therefore, this could be the best period to show a favorable effect of salbutamol. For the same reason, the need for COPD patients to use salbutamol as a rescue drug is expected to be more frequent in real life eight hours after a dose of formoterol.

The number of patients who completed the protocol was small. One third of patients dropped out for different reasons related to the length of the study. However, ten patients provided power of 80%, at the 5% significance level, to detect the same smallest clinically relevant difference of FEV₁ with the same standard deviation of difference in FEV₁ after bronchodilators. Nevertheless, we recognize that these results need to be confirmed in larger cohorts of COPD patients. However, to the best of our knowledge, this is the first study that investigated the effect of SABA in terms of dose-response curve in stable COPD patients regularly treated with LABA for a long period, eventually using SABA to control sporadic acute symptoms or during mild worsening of their symptoms and not in presence of acute exacerbations.

This was an observational study given that we could not include a group receiving placebo because of restrictions imposed by the local ethics committee arising from the duration of the study, but we believe that the reproducibility of FEV₁ and forced vital capacity which this study assesses has been reported frequently enough to make this unnecessary.²¹

To our knowledge, no clinical and functional data have presently been reported about the effects of acute SABA administration on top of regular LABA treatment in COPD patients. In light of our results, we believe that a study with indacaterol, for instance, should be carefully performed.

In conclusion, the results of the present study suggest that during chronic therapy with conventional doses of formoterol (inhaled as a dry powder) in moderate-to-severe COPD, the add-on use of salbutamol (by metered dose inhaler) does not improve peak expiratory flow and FEV₁ markedly, but is still effective in reducing air trapping, as shown by the increase in forced vital capacity and possibly dynamic pulmonary hyperinflation in the presence of tidal expiratory flow limitation at rest. However, these effects that are expected to diminish acute symptoms in COPD patients during long-term treatment with LABA, can be obtained with doses of salbutamol (by metered dose inhaler) higher than 400 µg.

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Disclosure

The authors report no conflicts of interest in this work.

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