

Effects on small airway obstruction of long-term treatments with beclomethasone/formoterol hydrofluoroalkane (metered-dose inhaler) versus fluticasone/salmeterol (dry-powder inhaler) in asthma: A preliminary study

Luciano Corda, M.D.,¹ Giovanni Gardini Gardenghi, M.D.,² Denise Modina, M.D.,² Luigi Taranto Montemurro, M.D.,² Mauro Novali, M.D.,² and Claudio Tantucci, M.D.²

ABSTRACT

New formulations of extrafine particles of long-acting beta-2 agonists plus inhaled corticosteroids (LABA + ICS) have been shown to reach peripheral regions of the lung. The aim of the study was to assess the effect on small airway obstruction of long-term treatments with two different LABA + ICS formulations in asthma. Ten subjects with moderate persistent asthma were enrolled. After a 4-week washout period they were treated in a randomized crossover design for 24 weeks with formoterol, 12 micrograms, and beclomethasone, 200 micrograms, hydrofluoroalkane (HFA; by metered-dose inhaler) b.i.d. (FB) or salmeterol, 50 micrograms, and fluticasone, 250 micrograms (by dry-powder inhaler), b.i.d. (SF). At baseline and at the end of each period subjects underwent an Asthma Control Test (ACT) and Pulmonary Function Testing. The N₂ phase III slope and closing volume (CV) during single-breath washout test and difference between the maximal expiratory flow rates with air and heliox at isovolume corresponding to 50% [$\Delta(\text{heliox-air})\text{MEF}_{50\%}$] were measured to assess changes on peripheral airways function. Two subjects dropped out and eight completed the study. After SF and FB, forced expiratory volume at 1 second (FEV₁; $p < 0.01$) and FEV₁/forced vital capacity (FVC; $p < 0.01$ for SF and $p < 0.05$ for FB) increased when compared with baseline. Although both FB and SF treatments slightly increased $\Delta(\text{heliox-air})\text{MEF}_{50\%}$ isovolume versus baseline, only after FB the N₂ phase III slope and CV decreased from $1.61 \pm 0.61\%/L$ to $1.35 \pm 0.49\%/L$ ($p = 0.054$) and from 0.98 ± 0.56 L to 0.88 ± 0.58 L ($p < 0.05$), respectively. ACT score raised from 19 ± 5 (baseline) to 23 ± 1 after FB ($p < 0.02$) and 23 ± 2 after SF ($p < 0.05$). When compared with baseline and in contrast to SF (50/250 micrograms b.i.d.), FB HFA (12/200 micrograms b.i.d.) significantly improved functional parameters reflecting small airway obstruction in asthmatic patients. Registered in the public trial registry at www.ClinicalTrials.gov identifier: NCT01255579.

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Bronchial asthma is a chronic inflammatory disease involving the whole respiratory tract. Inflammation in asthma affects not only the central airways but extends to the distal airways and even to lung parenchyma.¹ Both inflammation and remodeling occurring in peripheral airways of subjects with asthma have been established by immunocytochemistry and *in situ* hybridization studies.^{2–5} The inflammatory process in the small airways is similar to that observed in the large ones, but it is often more severe, involving the adventitia more than submucosal area.⁵

International guidelines recommend the use of long-acting β_2 -agonist plus inhaled corticosteroids (LABA + ICS) in asthmatic subjects who are not controlled by

ICS alone.⁶ Chlorofluorocarbon formulations produce relatively large particles (mass median aerodynamic diameter of $\sim 4 \mu\text{m}$), allowing good control of inflammation in the proximal airways.^{7,8} Because small airways may be the predominant site of obstruction in some phenotypes of bronchial asthma, however, new technologies have been developed to deliver drugs also to the distal bronchial tree. The new therapeutic hydrofluoroalkane (HFA) formulations of ICS with a mass median aerodynamic diameter of $< 1.1 \mu\text{m}$ have been shown to reach the peripheral airways with reduced deposition in the oropharynx.⁹ Thus, the use of these extrafine formulations inducing a more homogeneous drug distribution in the respiratory tract could potentially decrease inflammation in either large or small airways. Furthermore, these formulations need a lower total dose of ICS to be equipotent,¹⁰ possibly decreasing systemic side effects. The efficacy and tolerability of the new fixed combination of extrafine beclomethasone plus formoterol are similar to those of preexisting fixed associations of budesonide plus formoterol¹¹ and fluticasone propionate plus salmeterol,¹²

From the ¹Prima Divisione di Medicina Interna, Spedali Civili, Brescia, Italy, and ²Cattedra di Malattie dell'Apparato Respiratorio, Università degli Studi di Brescia, Italy

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Address correspondence and reprint requests to Luciano Corda, M.D., Prima Divisione di Medicina, Spedali Civili, Piazzale Spedali Civili, 1-25123 Brescia, Italy

E-mail address: luciano.corda@spedalicivili.brescia.it

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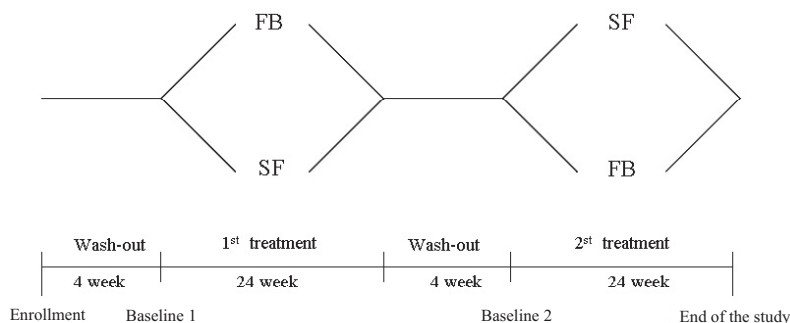


Figure 1. Flowchart of study design. FB, formoterol 12 µg plus beclomethasone hydrofluoroalkane (HFA) 200 µg, b.i.d.; SF, salmeterol 50 µg plus fluticasone propionate 250 µg Diskus b.i.d.

when looking at conventional lung function parameters. Nevertheless, although this new association appears to warrant a clinical advantage,^{11,12} its effect on small airways in asthma needs to be more deeply evaluated. The aim of this study was to assess and compare the effects on small airway obstruction of long-term treatments with formoterol plus beclomethasone (FB) HFA (12/200 µg, b.i.d.) versus salmeterol plus fluticasone propionate (SF; 50/250 µg b.i.d.) in subjects with moderate persistent asthma.

METHODS

Study Design

Eligible subjects had to be affected by moderate persistent bronchial asthma according to Global Initiative for Asthma guidelines,⁶ with no associated respiratory diseases and smoking history. Oral corticosteroid in the previous 6 months was not allowed. Enrolled child-bearing women must not be pregnant or become pregnant during the study.

After a 4-week washout period, during which patients were allowed to take only salbutamol (as needed), they were assigned according to a double-blind, double-dummy randomized crossover study to one of the two following 24-week treatments: (1) FB HFA (12/200 µg; by metered-dose inhaler) b.i.d. or (2) SF (50/250 µg; by dry-powder inhaler) b.i.d. Daily doses of 400 µg of beclomethasone HFA and 500 µg of fluticasone propionate are equivalent, according to the Global Initiative for Asthma International guidelines.⁶ At the end of the first period and after another 4-week washout period, they received the second randomized 24-week treatment (Fig. 1).

Adherence to the treatment was based on self-reports by each patient, on a declaration of willingness to continue to participate in the study, and on the counter of drug doses disposed by inhalers. All patients have been trained to correctly inhale the drugs by different devices. At the end of the washout periods and two treatments the subjects underwent an Asthma Control Test (ACT), oxygen saturation (SaO₂) measurement, and Pulmonary Function Testing. The subjects were enrolled after written consent was obtained. The

protocol has been approved by our local Ethics Committee.

Asthma Control Test

Subjects completed an ACT questionnaire at the end of each washout and treatment period. Asthma control was assessed by the validated Italian version of the ACT. They subjectively evaluated the degree of impairment caused by their asthma during the preceding 4 weeks answering five questions using a 5-point scale. The ACT is a reliable and validated tool, responsive to changes in asthma control over time. A cutoff score of ≤19 identifies subjects with poorly controlled asthma.¹³

Pulmonary Function Testing

A computerized water-sealed light-bell Stead-Wells spirometer (Biomedin, Padua, Italy) was used for measuring slow vital capacity (SVC), inspiratory capacity, and maximal flow-volume curves. The operator was assisted during the test by software that was able to verify electronically both the acceptability and the repeatability of spirometric maneuvers. All of the spirometric tests used in the study fulfilled the recommendations of American Thoracic Society.¹⁴ Total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) were obtained by using the plethysmographic method. The body plethysmograph was a variable flow, constant pressure type with a frequency response that was flat until 30 Hz (Biomedin).

Determination of the slope of N₂ phase III and closing volume (CV) was obtained during a single-breath nitrogen washout test¹⁵ (Medical Graphics, St. Paul, MN). Subjects in sitting position after exhaling to RV inhaled slowly pure oxygen with a single breath until TLC and then expired slowly from TLC to RV. The expired nitrogen concentration was measured and plotted as function of expired lung volume. This relationship was fitted linearly in the phase III, and the slope of N₂ phase III was computed automatically by the software. The onset of phase IV was identified on the trace by software or by visual examination, if required. The average values of the N₂ phase III slope

Table 1 Anthropometric and baseline (after 4-week washout periods) functional parameters of the subjects who were enrolled and who completed the study

	Subjects Enrolled (10)	Subjects Studied (8)	
Age (yr)	41 ± 11	45 ± 10	
Gender (M/F)	5/5	3/5	
BMI (Kg/m ²)	24 ± 3	24 ± 3	
		Baseline 1	Baseline 2
SVC (%pred)	120 ± 11	120 ± 13	119 ± 12
IC (%pred)	99 ± 16	98 ± 16	98 ± 15
FVC (%pred)	119 ± 10	117 ± 11	117 ± 10
FEV ₁ (%pred)	89 ± 20	84 ± 19	86 ± 18
MEF _{50%} (%pred)	46 ± 18	44 ± 19	43 ± 19
MEF _{25%} (%pred)	33 ± 13	32 ± 13	32 ± 14
FEV ₁ /FVC (%)	62 ± 12	61 ± 12	60 ± 12
FEV ₁ /SVC (%pred)	75 ± 16	72 ± 17	73 ± 16
TLC _{Pleth} (%pred)	118 ± 10	118 ± 11	118 ± 10
FRC _{Pleth} (%pred)	131 ± 21	132 ± 22	132 ± 21
RV _{Pleth} (%pred)	113 ± 19	113 ± 19	113 ± 18
RV/TLC %	32 ± 7	32 ± 7	30 ± 5
SpO ₂ %	96 ± 2	96 ± 2	96 ± 2
ACT (score)	19 ± 5	19 ± 5	19 ± 5

Values are mean ± SD.

BMI = body mass index; M = male; F = female; BMI = body mass index; % pred = percent predicted; SVC = slow vital capacity; IC = inspiratory capacity; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the 1st s; MEF_{50%} = maximal expiratory flow at 50% of the forced vital capacity; MEF_{25%} = maximal expiratory flow at 25% of the forced vital capacity; TLC_{Pleth} = total lung capacity assessed by plethysmography; FRC_{Pleth} = functional residual capacity assessed by plethysmography; RV_{Pleth} = residual volume assessed by plethysmography; SpO₂ = oxygen saturation; ACT = Asthma Control Test.

and CV obtained from two acceptable and reproducible measurements (with expiratory SVC within 10%) were selected for analysis.

Expiratory maximal flow-volume curves, breathing either air or heliox (oxygen 21% and helium 79%), were also performed. Breathing mixture was introduced in the bell of the spirometer by a three-way stopcock connected to the ambient air or to a cylinder containing humidified heliox at ambient temperature and pressure. In each occasion, after 3 slow deep breaths to TLC, a forced expiratory maneuver was performed starting from TLC without end-inspiratory pause. Measurements of maximal expiratory flow rate at 50% of the forced vital capacity (MEF_{50%}) with air and heliox and determination of their differences [$\Delta(\text{heliox-air})\text{MEF}_{50\%}$] were obtained at baseline and subsequently at corresponding isovolume.

Statistical Analysis

All values are expressed as mean ± SD. We used the mean of the functional values of the two baselines for comparisons. Analysis of variance of the variables of interest among baseline and two therapeutic regimens (end of treatment periods) were performed by Fried-

man's test. Comparisons between groups were made according to Wilcoxon test, when allowed. A value of $p < 0.05$ was considered significant. Statistical analysis was performed with GraphPad Prism Version 4 (GraphPad Software, San Diego, CA).

RESULTS

Ten subjects (five men) were enrolled in the study. Two of them (two women) dropped out because of low adherence to the treatment (at weeks 8 and 31, respectively), and eight subjects (three men; mean age, 45 ± 10 years; body mass index, 24 ± 3 kg/m²) completed the study. Anthropometric and functional parameters of the subjects after the two 4-week washout periods are shown in Table 1. The functional values of the two baselines were almost identical.

Forced expiratory volume at 1 second (FEV₁) significantly increased after both SF (100 ± 13% predicted [pred.]) and FB (99 ± 11% pred.) when compared with baseline (84 ± 21% pred.; $p < 0.01$; Table 2). The FEV₁/forced vital capacity (FVC) ratio was significantly greater both after SF (68 ± 8%) and FB (67 ± 9%) when compared with baseline (60 ± 8%; $p < 0.01$ and $p < 0.05$ for SF and FB, respectively; Table 2). The

Table 2 Comparison of functional parameters at baseline and after the two 24-wk periods of treatment

	Mean Baseline	24-wk SF		24-wk FB	
		Mean $\pm$ SD	<i>p</i> vs Baseline	Mean $\pm$ SD	<i>p</i> vs Baseline
SVC (%pred)	120 $\pm$ 13	124 $\pm$ 13	n.s.	124 $\pm$ 15	n.s.
IC (%pred)	98 $\pm$ 16	100 $\pm$ 13	n.s.	115 $\pm$ 10	n.s.
FVC (%pred)	117 $\pm$ 11	125 $\pm$ 14	n.s.	125 $\pm$ 15	n.s.
FEV ₁ (%pred)	84 $\pm$ 21	100 $\pm$ 13	<0.01	99 $\pm$ 11	<0.01
MEF _{50%} (%pred)	44 $\pm$ 19	60 $\pm$ 16	<0.01	59 $\pm$ 23	<0.01
MEF _{25%} (%pred)	32 $\pm$ 13	43 $\pm$ 13	<0.01	40 $\pm$ 15	<0.05
FEV ₁ /FVC (%)	60 $\pm$ 8	68 $\pm$ 8	<0.01	67 $\pm$ 9	<0.05
FEV ₁ /SVC (%pred)	72 $\pm$ 19	82 $\pm$ 10	n.s.	82 $\pm$ 11	n.s.
TLC _{Pleth} (%pred)	118 $\pm$ 11	118 $\pm$ 12	n.s.	119 $\pm$ 13	n.s.
FRC _{Pleth} (%pred)	132 $\pm$ 22	142 $\pm$ 31	n.s.	135 $\pm$ 23	n.s.
RV _{Pleth} (%pred)	113 $\pm$ 19	113 $\pm$ 16	n.s.	114 $\pm$ 12	n.s.
RV/TLC %	31 $\pm$ 7	30 $\pm$ 6	n.s.	30 $\pm$ 6	n.s.
$\Delta_{(\text{heliox-air})}$ MEF _{50%} (L/s)	0.36 $\pm$ 0.17	0.49 $\pm$ 0.31	n.s.	0.64 $\pm$ 0.30	0.07
FVC/SVC %	94 $\pm$ 4	98 $\pm$ 3	0.05	98 $\pm$ 1	0.07
Phase III slope (N ₂ %/L)	1.61 $\pm$ 0.61	1.48 $\pm$ 0.86	n.s.	1.35 $\pm$ 0.49	0.054
CV (L)	0.98 $\pm$ 0.56	0.96 $\pm$ 0.56	n.s.	0.88 $\pm$ 0.58	<0.05
CC (L)	3.08 $\pm$ 1.17	2.98 $\pm$ 1.07	n.s.	2.90 $\pm$ 1.00	n.s.
SpO ₂ %	96 $\pm$ 2	97 $\pm$ 1	n.s.	97 $\pm$ 1	n.s.
ACT (score)	19 $\pm$ 5	23 $\pm$ 1	<0.05	23 $\pm$ 2	<0.02

Values are mean $\pm$ SD.

FB = formoterol 12 μ g and beclomethasone 200 μ g hydrofluoroalkane (HFA) (2 puffs by metered dose inhaler [MDI]) b.i.d.; SF = salmeterol 50 μ g and fluticasone 250 μ g (Diskus) b.i.d.; %pred = percent predicted; SVC = slow vital capacity; IC = inspiratory capacity; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the 1st s; MEF_{50%} = maximal expiratory flow at 50% of the forced vital capacity; MEF_{25%} = maximal expiratory flow at 25% of the forced vital capacity; TLC_{Pleth} = total lung capacity assessed by plethysmography; FRC_{Pleth} = functional residual capacity assessed by plethysmography; RV_{Pleth} = residual volume assessed by plethysmography; $\Delta_{(\text{heliox-air})}$ MEF_{50%} = difference between the maximal expiratory flow rates with air and heliox at isovolume corresponding to 50% of the baseline forced vital capacity; Phase III slope = slope of N₂ phase III closing volume measurement; CV = closing volume; CC = closing capacity; SpO₂ = arterial oxygen saturation; ACT = Asthma Control Test.

FVC/SVC ratio was higher after SF (98 $\pm$ 3%; *p* = 0.05) and after FB (98 $\pm$ 1%; *p* = 0.07) when compared with baseline (94 $\pm$ 4%; Fig. 2). MEF_{50%} was significantly higher after SF (60 $\pm$ 16%; *p* < 0.01) and after FB (59 $\pm$ 23%; *p* < 0.01). Maximal expiratory flow rate at 25% of the FVC (MEF_{25%}) was significantly higher after SF (43 $\pm$ 13%; *p* < 0.01) and after FB (40 $\pm$ 1%; *p* < 0.05). After either treatment $\Delta_{(\text{heliox-air})}$ MEF_{50%} at isovolume increased from 0.36 $\pm$ 0.17 L/s at baseline to 0.49 $\pm$ 0.31 L/s after SF (n.s.) and was slightly better after FB to 0.64 $\pm$ 0.30 L/s (*p* = 0.07; Table 2 and Fig. 2).

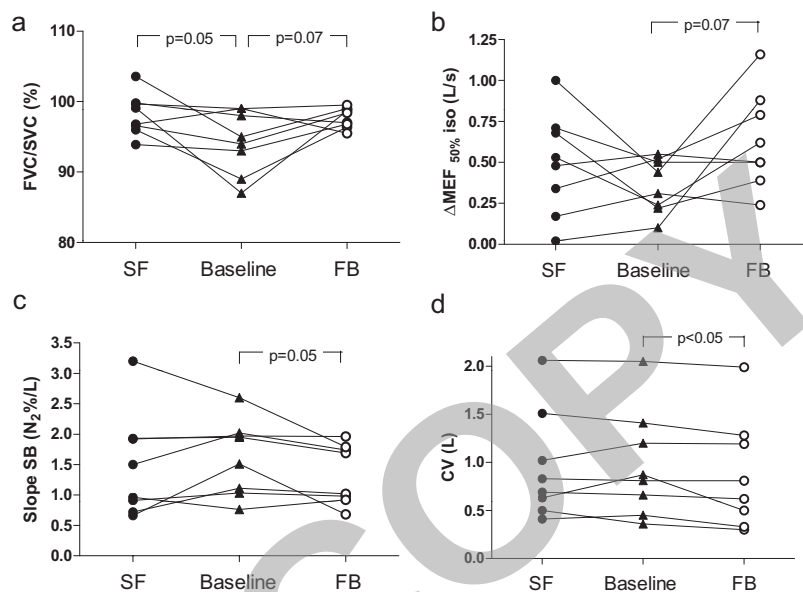
With respect to baseline, during single-breath nitrogen washout test the N₂ phase III slope and CV decreased after FB, from 1.61 $\pm$ 0.61 N₂%/L to 1.35 $\pm$ 0.49 N₂%/L (*p* = 0.054) and from 0.98 $\pm$ 0.56 L to 0.88 $\pm$ 0.58 L (*p* < 0.05), respectively; in contrast, after SF the N₂ phase III slope and CV did not show a significant reduction from 1.61 $\pm$ 0.61 N₂%/L to 1.48 $\pm$ 0.86 N₂%/L (n.s.) and from 0.98 $\pm$ 0.56 L to 0.96 $\pm$ 0.56 L (n.s.), respectively (Table 2 and Fig. 2).

ACT score was raised from 19 $\pm$ 5 at baseline to 23 $\pm$ 2 for FB (*p* < 0.02) and 23 $\pm$ 1 for SF (*p* < 0.01), respectively (Table 2). No significant difference between two treatments was found after 24 weeks in any functional parameter assessed. No side effects caused by the two treatments were reported by patients.

DISCUSSION

In this study the effect of long-term treatments with two different LABA + ICS formulations was assessed in patients with moderate persistent asthma, mainly looking at changes of functional parameters recognized as useful to explore the small airway function. The combination with extrafine FB significantly decreased CV and induced a nearly significant decrease in the slope of N₂ phase III and an increase of $\Delta_{(\text{heliox-air})}$ MEF_{50%} at isovolume. These indices were not improved with SF given at equipotent dose. Such findings suggest that extrafine formulations of LABA and ICS

Figure 2. Comparisons with baseline of values obtained after the two treatments for (a) FVC/SVC, (b) $\Delta\text{MEF}_{50\%\text{iso}}$, (c) slope of N_2 phase III of single-breath N_2 washout test (slope SB = phase III slope), and (d) CV. SF, salmeterol 50 μg plus fluticasone propionate 250 μg b.i.d.; FB, formoterol 12 μg plus beclomethasone hydrofluoroalkane (HFA) 200 μg b.i.d.; CV, closing volume; FVC, forced vital capacity; SVC, slow vital capacity; $\Delta\text{MEF}_{50\%\text{iso}}$, difference between the maximal expiratory flow rates with air and heliox at isovolume corresponding to 50% of the baseline forced vital capacity.



not only can reach the peripheral airways (<2 mm in diameter) but also may have beneficial effects on the distal inflammation with consequent improvement of small airway caliber and function.

Similar results were recently reported in 30 patients with moderate asthma showing that the group randomized to extrafine FB HFA (12/200 μg b.i.d.) had a nearly significant decrease of closing capacity after a 12-week period of treatment when compared with baseline, and no reduction was observed in the group assuming SF (50/250 μg b.i.d.).¹⁶ These two preliminary and distinct observations together with other studies^{17,18} strongly encourage the planning of multicenter randomized clinical trials to compare, in a larger population of asthmatic subjects with peripheral airway involvement, extrafine LABA + ICS formulations versus equipotent standard LABA + ICS combinations. The purpose is to firmly establish if extrafine LABA + ICS formulations can control effectively small airway inflammation better than standard fixed LABA + ICS combinations in such a phenotype of asthma.

As previously shown,¹² extrafine FB HFA (12/200 μg b.i.d.) was equally effective in increasing peak expiratory flow, FEV_1 , and FEV_1/FVC when compared with SF combination. Moreover, the ACT score was also significantly and equally improved with both treatments. Our data confirm a marked bronchodilating and anti-inflammatory effects of extrafine FB HFA (12/200 μg b.i.d.) also on larger airways¹⁶ and an optimal clinical control of the disease in patients with moderate persistent asthma, which are not dissimilar from those obtained with usual LABA + ICS combinations.^{11,12}

In contrast with SF (50/250 μg b.i.d.), the long-term treatment with extrafine FB HFA (12/200 μg b.i.d.), however, was found to significantly reduce CV and

nearly significantly reduce the slope of N_2 phase III, when compared with baseline. The reduction of CV, despite the mild SVC increase, implies a much later closure of dependent small airways during slow exhalation toward RV. In line with another previous observation,¹⁶ these findings may likely reflect an effective bronchodilating and anti-inflammatory activity elicited on peripheral airways by prolonged assumption of extrafine FB HFA. Less risk of tidal-dependent airway closure and better gas exchange, especially in the supine position, are possible beneficial effects after CV reduction. Moreover, higher CV and closing capacity in asthmatic patients have been associated with more frequent and severe exacerbations¹⁹ and a treatment effective on controlling these parameters might be clinically useful in these difficult to control asthma patients.

The lower slope of N_2 phase III indicates a less heterogeneous lung emptying, suggesting a more narrow distribution of expiratory regional time constants of the lung. This has been ascribed to a decrease in peripheral airway resistance with less asynchronous and unequal distribution of peripheral ventilation and could partly explain the reduction of airway responsiveness²⁰ that has been previously reported with the use of both extrafine LABA + ICS¹⁶ and extrafine ICS formulations.²¹

Finally, it is important to stress the improvement in the $\Delta(\text{heliox-air})\text{MEF}_{50\%}$ at isovolume obtained by the extrafine FB HFA which, was higher than that observed with the conventional LABA + ICS formulation and nearly significantly higher when compared with baseline (Fig. 2). Much greater is the increment of maximal expiratory flow rates with heliox (as compared with air), much closer to larger airways (where the flow is turbulent) is the principal site of airflow resistance, as normally

occurs in healthy subjects. The increase of this difference, usually measured as $MEF_{50\%}$ at isovolume, reflects a relatively greater influence of central airway resistance on the maximal expiratory flow, which corresponds to a lesser contribution of peripheral airway resistance. Therefore, the change found in $\Delta(\text{heliox-air})MEF_{50\%}$ at isovolume indirectly supports an increase in the small airway caliber, which appears more marked, when compared with baseline, after the treatment with extrafine LABA + ICS formulation.

As expected in a pilot study, the small number of patients is clearly a limit in the interpretation of the data because a type II error could mask the potential significance of the differences of both treatments versus baseline and also between treatments. In addition, the patients have mild baseline airflow obstruction and were not “*a priori*” chosen with functional impairment of small airways, as generally shown by abnormally increased RV, markedly reduced FVC/SVC ratio, high CV and closing capacity, and/or a steeper slope of N_2 phase III. Despite the few patients studied and unselected for a prevalent involvement of peripheral airways, the parameters related to small airway obstruction showed already significant or nearly significant improvement with extrafine FB administration in respect to baseline, which was not the case after equipotent SF treatment. In conclusion, when compared with baseline and in contrast to SF (50/250 μg b.i.d.), FB HFA (200/12 μg b.i.d.) appears to significantly improve functional parameters reflecting small airway obstruction in asthmatic patients.

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