

The functional benefit of anti-inflammatory aerosols in the lung periphery

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Background: The target of anti-inflammatory therapy in asthma is thought to be situated, at least partly, in the lung periphery, and inhaled steroid aerosols are being engineered to reach it. However, the potential effect of such aerosols cannot be fully evaluated by conventional lung function tests because these are insensitive to peripheral lung structure.

Objective: A prospective cohort study was conducted to investigate whether ultrafine steroid aerosols can elicit a response in the lung periphery, using a validated multibreath washout technique that can distinguish acinar from conductive lung zone function.

Methods: In 30 stable patients with asthma with a wide range of disease severity (FEV₁ 27% to 108% predicted), we assessed conductive and acinar airway function abnormality at baseline, with patients on a standard dry powder steroid aerosol and after switching them to an ultrafine steroid aerosol.

Results: Only in those patients with abnormal acinar airway function at baseline (n = 16) did acinar heterogeneity show a consistent improvement after switching to an ultrafine steroid aerosol; the improvement was also correlated with baseline acinar heterogeneity ($r = -0.67$; $P = .007$). Although all patients with asthma also presented conductive airway abnormality at baseline, no changes were observed in this lung zone with the switch to the ultrafine aerosol ($P > .1$).

Conclusion: Among stable patients with asthma, those with acinar lung zone abnormality at baseline have the potential to receive functional benefit from an ultrafine steroid aerosol.

Clinical studies comparing the efficacy of steroid aerosols targeted to the deep lung should at least include a measurement of peripheral lung zone function.

Clinical implications: A new noninvasive measure of small airways function reveals why, and for which particular patients with asthma, small steroid aerosol particles can be of therapeutic use. (*J Allergy Clin Immunol* 2006;118:340-6.)

Key words: Asthma, small airways, inhaled corticosteroids, ultrafine aerosols

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Abbreviations used

AQLQ:	Asthma Quality of Life Questionnaire
BDP:	Beclomethasone dipropionate
BUD:	Budesonide
CFC:	Chlorofluorocarbon
DL _{CO} :	Carbon monoxide diffusing capacity
DPI:	Dry powder inhaler
FEF ₇₅ :	Forced expiratory flow after exhalation of 75% forced vital capacity
FEF ₂₅₋₇₅ :	Forced expiratory flow between exhalation of 25% and 75% forced vital capacity
FRC _{mbw} :	Multiple breath washout derived functional residual capacity
FRC _{pl} :	Plethysmographic functional residual capacity
FVC:	Forced vital capacity
HFA:	Hydrofluoroalkane
MBW:	Multiple breath washout
MMAD:	Median mass aerodynamic diameter
RV _{pl} :	Plethysmographic residual volume
Sacin:	Multiple breath washout derived index of acinar ventilation heterogeneity
Scond:	Multiple breath washout derived index of conductive ventilation heterogeneity
sGaw:	Specific airway conductance
TLC _{pl} :	Plethysmographic total lung capacity

Inhaled corticosteroids are the mainstay in therapy of patients with persistent asthma.¹ In the past decade, considerable efforts have been directed toward the development of aerosol formulations and delivery devices that could target corticosteroids to the lung periphery. This target is based on pathophysiological observations of inflammation in the small airways and lung parenchyma in asthma.² One of the obvious ways, at least in theory, to promote peripheral deposition of aerosol particles or droplets is to render them smaller. Such an opportunity appeared when chlorofluorocarbon (CFC) propellants needed phasing out and a hydrofluoroalkane (HFA)–driven beclomethasone dipropionate (BDP) aerosol was produced containing droplets with a median mass aerodynamic diameter (MMAD) of approximately 1 μ m,³ in contrast with other press-and-breathe steroid aerosols with MMAD typically ranging from 2 to 4 μ m.⁴

Scintigraphy studies have demonstrated more than 50% lung deposition of HFA-BDP aerosols in healthy

volunteers and in patients with asthma³⁻⁵ with a preferential distribution toward peripheral air spaces.⁵ Comparative clinical studies using spirometric indices have indicated that only half the HFA-BDP dose suffices to obtain similar or better therapeutic efficacy than the standard inhaled steroids⁶⁻¹² with no clinically relevant systemic side effects for daily HFA-BDP doses below 800 μ g.¹³ Several studies have attempted to assess the effect of HFA-BDP on small airway function.^{6,10,14-17} Improvements in end-expiratory flows were observed when HFA-BDP was added to the baseline steroid treatment of patients with poorly controlled asthma,¹⁴ or when steroid-naïve patients with asthma were given HFA-BDP.¹⁰ However, when comparing the effect of half dose HFA-BDP with budesonide delivered from a dry powder inhaler,^{6,15} end-expiratory flow improvements were found to be similar for both. Busse et al¹⁶ reported a shift to the left of the HFA-BDP versus the CFC-BDP dose-response curve for forced expiratory flow between exhalation of 25% and 75% forced vital capacity (FEF₂₅₋₇₅). Finally, Goldin et al¹⁷ used lung attenuation curves from high resolution computed tomography to show less air trapping with HFA-BDP versus CFC-BDP, yet the exact contribution from conductive versus acinar airways remains obscure.

Although Marshall et al¹⁸ have shown a greater potential for an anti-inflammatory effect on an *ex vivo* alveolar macrophage preparation when inhaled steroids had been delivered via HFA-BDP versus CFC-BDP aerosols, the functional benefit of the acinar airways peripheral to the first 150 mL of conductive airways has never been assessed. With the low resistance of the acinar lung zone impeding conventional spirometry to provide a noninvasive marker of the acinar lung structure, ventilation distribution tests offer a valuable alternative. Indeed, the multiple breath washout (MBW) and its normalized phase III slope analysis have been successfully used to quantify and separate conductive from acinar ventilation heterogeneity, reflecting their respective airway structures.¹⁹⁻²² It has been shown that, in contrast with the acinar airways, the small conductive airways invariably show an abnormality that cannot be fully reversed to normal with a β -agonist even in mild asthma.²⁰ Patients with moderate to severe asthma were characterized by an abnormality in both the conductive and acinar airways, neither of which could be fully reversed to normal with a β -agonist.²¹

The current study aims to characterize the baseline functionality of conductive and acinar airways compartments in stable patients with asthma with a wide range of severity, and to assess their response to a steroid aerosol that is expected to deposit, at least in part, in the acinar lung zone. We hypothesized that patients with asthma with normal acinar airways function at baseline will not particularly gain from switching from budesonide (BUD) delivered from a dry powder inhaler (DPI) to an ultrafine HFA-driven BDP aerosol. By contrast, patients with more severe asthma with a distinct acinar abnormality are expected to respond favorably and improve acinar ventilation heterogeneity.

METHODS

Patients

The study protocol was approved by the local ethics committee. The 30 patients (19 M/11 F) participating in this study had a clinical history of asthma (>2 years) and had shown, in the 2-year period before testing, a positive histamine provocation test or a baseline obstruction with >10% predicted FEV₁ reversibility. All patients with asthma were atopic; all were never-smokers. None of the patients had any exacerbation in the 6-month period before the study, and all patients had been carefully titrated to the appropriate dose of inhaled steroids.¹ At inclusion, all patients were on stable maintenance treatment for at least 6 weeks using dry powder budesonide (Pulmicort Turbuhaler; AstraZeneca, Lund, Sweden); daily doses were 200 μ g (n = 13), 400 μ g (n = 13), or 800 μ g (n = 4). Twenty patients were also using long-acting β -agonists, and all patients used salbutamol as rescue medication. After giving written informed consent, all patients were requested not to take any β -agonist medication for at least 24 hours before the time of study, when a baseline measurement was made, labeled DPI-BUD. On this baseline visit, all patients filled out an Asthma Quality of Life Questionnaire (AQLQ).²³ After having been instructed on how to adequately use the QVAR Autohaler device (UCB, Brussels, Belgium), patients took HFA-BDP at the same BDP dose as the BUD dose in their DPI-BUD device for 6 weeks, and another measurement was made, labeled HFA-BDP_(1/1). Then, this HFA-BDP dose was halved and taken for another 6 weeks, and a final measurement was obtained, labeled HFA-BDP_(1/2). The latter measurement was only performed because the recommended dose of this formulation is generally thought to be equivalent to half the DPI-BUD dose (ie, a recommendation based on studies that do not include small airways function assessment). Each of the 3 visits was planned at the same time of day to minimize intrasubject diurnal variability and included reversibility testing with a total dose of 400 μ g salbutamol via an antistatic coated spacer under strictly controlled conditions.²⁰

Procedures

Spirometry was obtained by means of standardized equipment (Vmax 20C; SensorMedics, Bilthoven, The Netherlands). From the forced expiratory curve, we used FEV₁, forced vital capacity (FVC), forced expiratory flow after exhalation of 75% FVC (FEF₇₅), and FEF₂₅₋₇₅; predicted values for FEV₁, FEF₂₅₋₇₅, and FEF₇₅ were based on those provided by the European Community for Steel and Coal. From the subsequent forced inspiration, peak inspiratory flow was recorded. Single-breath carbon monoxide diffusing capacity (DL_{CO}) was also obtained from standard lung function equipment (Model 2200; SensorMedics). Finally, we also measured specific airway conductance (sGaw), plethysmographic residual volume (RV_{pl}), functional residual capacity (FRC_{pl}), and total lung capacity (TLC_{pl}; Model 6200; SensorMedics).

The ventilation distribution test or MBW was performed by using a computer-controlled bag-in-box breathing assembly. Instrumentation and underlying theory of ventilation distribution tests have been extensively reported and validated elsewhere.¹⁹ Tidal volume was targeted at 1 L, and after a period of air breathing with stable end-expiratory lung volume at functional residual capacity, inspired air was switched to the test gas mixture. The test gas mixture consisted of pure O₂, and 1 L tidal breathing continued for 20 to 25 breaths depending on the subject's lung volume (dilution); exhaled N₂ concentration traces were analyzed.

From the MBW N₂ trace, indices Scond and Sacin were derived to represent the conductive and acinar components of ventilation heterogeneity, respectively, using an analysis that can be summarized as follows. During each expiration, the N₂ phase III slope

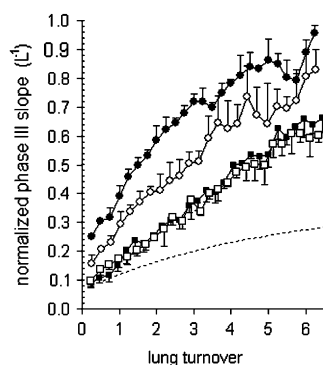


FIG 1. Normalized phase III slopes as a function of lung turnover in 2 patients with asthma (circles and rectangles) at baseline (DPI-BUD; solid symbols) and after HFA-BDP_(1/1) (open symbols); a typical normal curve is also represented for comparison (dotted line).

is computed and normalized by the mean expired N_2 concentration. This leads to an increasing normalized slope as a function of breath number or lung turnover; lung turnover is determined as the cumulative expired volume divided by ventilated functional residual capacity (FRC_{mbw}), which is computed from a mass balance of the MBW test. Fig 1 shows typical normalized slope versus lung turnover curves obtained in 2 patients with asthma before (solid symbols) and after (open symbols) the switch from DPI-BUD to HFA-BDP_(1/1); the dotted line is a curve typical of a normal subject. On theoretical grounds, it can be shown that (1) the rate of rise of the curve is a result of the convective flow asynchrony between lung units larger than acini as a result of heterogeneity originating in the conductive airways, and (2) the offset of the curve is largely determined by diffusion-convection dependent heterogeneity generated in the acinar airways. Hence, Scond is simply computed as the rate of normalized phase III slope increase as a function of lung turnover, between 1.5 and 6 lung turnovers. Then, Sacin is computed as the normalized phase III slope of the first MBW expiration minus a correction term to discard any conductive lung zone contribution; this correction term equals the lung turnover corresponding to the first breath, multiplied by Scond.

The dotted curve in Fig 1 corresponds to $S_{cond} = 0.029 \text{ L}^{-1}$ (ie, roughly 0.27 L^{-1} minus 0.14 L^{-1} divided by 6 minus 1.5 turnovers) and to $S_{acin} = 0.073 \text{ L}^{-1}$ (ie, roughly 0.08 L^{-1} minus Scond times 0.25 turnovers); note that because lung turnover is a dimensionless parameter, Sacin and Scond coincidentally have the same dimension (L^{-1}). Normal ranges are $S_{acin} < 0.120 \text{ L}^{-1}$ and $S_{cond} < 0.042 \text{ L}^{-1}$, as determined on the basis of control values we recently obtained from a group of 63 normal never-smokers without bronchial hyperresponsiveness to histamine ($S_{acin} = 0.072 \pm 0.025(\text{SD})\text{L}^{-1}$; $S_{cond} = 0.028 \pm 0.007(\text{SD})\text{L}^{-1}$)²² with the cutoff for abnormality corresponding to the mean Sacin or Scond plus 1.96 times its SD. In the patient with asthma with the greater normalized slopes in Fig 1 (circles), $S_{acin} = 0.228 \text{ L}^{-1}$ when on DPI-BUD (solid circles) and Sacin decreases to 0.133 L^{-1} after the switch to HFA-BDP_(1/1) (open circles), whereas the Scond value remains essentially the same at an average 0.094 L^{-1} . In the patient with the smaller normalized slopes in Fig 1 (squares), Sacin and Scond remained essentially unaltered after the switch from DPI-BUD to HFA-BDP_(1/1), with average Sacin = 0.070 L^{-1} and Scond = 0.095 L^{-1} .

The theory of MBW phase III slope analysis leading to indices Scond and Sacin implies that ventilation heterogeneity can be attributed to different lung depths—that is, to the conductive and acinar lung zone, respectively, and that Scond and Sacin are intrinsically independent and are not comparable between each other

(despite having the same dimension, L^{-1}).¹⁹ Finally, because Scond and Sacin are derived from phase III slopes, their value increases when ventilation heterogeneity increases. In particular, Sacin will increase if ventilation heterogeneity is increased in the acinar lung zone, because of an alteration of the intra-acinar asymmetry (eg, unequal lumen narrowing of inflamed respiratory bronchioles). On the other hand, Scond will increase when heterogeneous narrowing of conductive airways induces an alteration in the specific ventilation and/or flow asynchrony between the lung units subtended by these airways proximal to the terminal bronchioles.

Statistical analysis

Using Statistica 5.5 (StatSoft, Tulsa, Okla), 1-way repeated-measures ANOVA tests were used to detect differences in all MBW and pulmonary function variables among the 3 visits (DPI-BUD, HFA-BDP_(1/1), HFA-BDP_(1/2)). Bonferroni adjustment was used to test for post hoc differences with a significance level set at $P = .05$. Pearson correlation analyses were also performed.

RESULTS

The 30 patients with asthma participating in this study showed a wide range in age (17–77 years; average, 43 ± 3 [SEM] years) and baseline FEV₁ value (27% to 108% predicted; average, 75 ± 4 (SEM) % predicted). At baseline, the patients' average AQLQ score was 5.68 ± 0.13 (SEM; on a scale of 1–7), and average baseline FEV₁/FVC was 65 ± 3 (SEM) %. Peak inspiratory flow averaged 5.3 ± 0.4 (SEM) L/s, attesting to the patients' capability to correctly operate the DPI-BUD device. Table I shows the average values of all relevant indices of lung function and ventilation heterogeneity, for the baseline visit when all patients were receiving DPI-BUD, for the second visit when patients had switched to HFA-BDP at full BDP dose for 6 weeks (HFA-BDP_(1/1)), and for the last visit after patients had switched to half the BDP dose for another 6 weeks (HFA-BDP_(1/2)). On each visit, lung function and ventilation heterogeneity were measured before and after bronchodilation with 400 μg salbutamol. When considering the patient group as a whole ($n = 30$), ANOVAs on all parameters of Table I showed a small but significant change in FEV₁, and no significant changes in the spirometric indices thought to reflect small airways function (FEF₇₅ or FEF_{25–75}). The only ventilation heterogeneity index showing a consistent gradual improvement with the switch to HFA-BDP on subsequent visits was Sacin. Indeed, after HFA-BDP_(1/1), Sacin decreased, although not significantly ($P = .07$), but after HFA-BDP_(1/2), its 18% decrease became significant ($P = .009$).

We then separated the patients with asthma into 2 groups on the basis of their Sacin values at baseline (DPI-BUD), using the aforementioned cutoff for abnormality at $S_{acin} = 0.12 \text{ L}^{-1}$. This cutoff divided the entire asthma group into an abnormal Sacin group ($n = 16$) and a normal Sacin group ($n = 14$). The resulting plots of baseline and postdilation Sacin and Scond in those 2 subgroups are shown in Fig 2, which also indicates the $S_{acin} = 0.12 \text{ L}^{-1}$ cutoff for abnormality in (A, horizontal solid line). From the symbols connected by dotted lines (normal

TABLE I. Changes in lung function and ventilation distribution when switching from DPI-BUD to HFA-BDP†

	DPI-BUD		HFA-BDP _(1/1)		HFA-BDP _(1/2)	
	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol
FEV ₁ (%pred)	75.1 ± 4.0	83.1 ± 4.3	76.8 ± 3.5	85.1 ± 4.0	77.3 ± 3.8	85.9 ± 4.0*
FEF ₇₅ (%pred)	39.7 ± 4.7	50.9 ± 6.5	41.7 ± 4.7	54.0 ± 6.6	40.0 ± 5.1	51.4 ± 6.7
FEF ₂₅₋₇₅ (%pred)	47.1 ± 5.1	59.1 ± 6.4	48.3 ± 4.8	61.5 ± 6.4	46.3 ± 5.1	58.7 ± 6.4
DLco (%pred)	91.7 ± 3.5	91.5 ± 3.1	92.0 ± 2.6	92.9 ± 2.7	94.5 ± 2.9	94.8 ± 2.7
sGaw (L/s/cmH ₂ O/L)	0.078 ± 0.009	0.133 ± 0.015	0.083 ± 0.009	0.126 ± 0.014	0.078 ± 0.008	0.129 ± 0.015
RV _{pl} (mL)	2552 ± 196	2312 ± 170	2435 ± 199	2296 ± 183	2330 ± 166	2130 ± 164
FRC _{pl} (mL)	3718 ± 233	3440 ± 209	3559 ± 224	3389 ± 219	3610 ± 204	3258 ± 201
TLC _{pl} (mL)	6264 ± 248	6156 ± 241	6163 ± 257	6152 ± 249	6222 ± 253	6115 ± 253
Sacin (L ⁻¹)	0.181 ± 0.028	0.158 ± 0.026	0.157 ± 0.021	0.145 ± 0.023	0.148 ± 0.020†	0.141 ± 0.021
Scond (L ⁻¹)	0.065 ± 0.005	0.055 ± 0.004	0.063 ± 0.005	0.053 ± 0.005	0.066 ± 0.006	0.052 ± 0.004
FRC _{mbw} (mL)	3236 ± 165	3111 ± 175	3201 ± 188	3029 ± 171	3182 ± 175	3066 ± 185

†DPI-BUD, after 6 weeks of budesonide dry powder inhaler; HFA-BDP_(1/1), after 6 weeks of ultrafine beclomethasone at equivalent dose; HFA-BDP_(1/2), after another 6 weeks of ultrafine beclomethasone at half dose. Data shown are averages ± SEMs; significant change from DPI-BUD: **P* < .05; †*P* < .01.

Sacin subgroup), it can be seen that neither Sacin nor Scond values corresponding to this group were significantly modified after switching from DPI-BUD to HFA-BDP. By contrast, the baseline Sacin in the abnormal Sacin group was considerably reduced (ie, improved) both after 6 weeks of HFA-BDP and after another 6 weeks of HFA-BDP at half dose, whereas Scond remained unaffected. Considering the normal Sacin value of 0.072 L⁻¹, respective Sacin decreases after HFA-BDP_(1/1) and HFA-BDP_(1/2) represent a 25% ([0.27-0.22]/[0.27-0.072]) and 30% ([0.27-0.21]/[0.27-0.072]) decrease of baseline Sacin abnormality.

Table II summarizes the characteristics of the 2 Sacin-based subgroups, showing a striking difference in mean age between both (*P* < .001), but no difference in AQLQ score or medication dose. At DPI-BUD, all spirometric parameters were smaller and some plethysmographic lung volumes were greater in the abnormal Sacin subgroup. After switching to the ultrafine aerosol, only RV_{pl} (significant at HFA-BDP_(1/2)) and Sacin (significant at HFA-BDP_(1/1) and HFA-BDP_(1/2)) were seen to improve significantly in this subgroup; note that the significant changes for Sacin are those corresponding to the baseline data of Fig 2 (solid circles). In the normal Sacin subgroup, none of the parameters in Table II showed any significant change on switching to HFA-BDP.

We assessed the actual relationship between lung function at baseline (ie, with patients on DPI-BUD) and its change after switching to HFA-BDP. This was performed for all variables in Table I, using data from either the entire group (*n* = 30) or the abnormal Sacin subgroup (*n* = 16). The only parameter showing a significant correlation within the latter subgroup, where regression was not artificially amplified by the cluster of normal data points in the entire group, was Sacin. Fig 3 shows the individual data points of the relationship between Sacin at baseline and the ΔSacin after switching to HFA-BDP at full dose (solid circles and solid line for abnormal Sacin subgroup correlation; *R* = -0.67; *P* = .007) and at half dose (solid

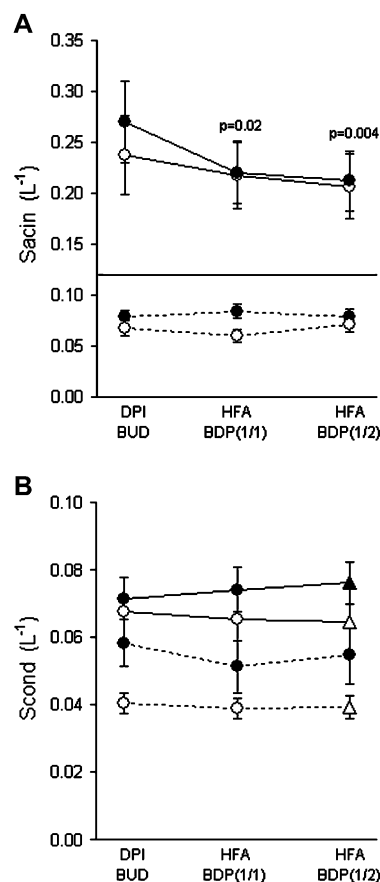


FIG 2. A, Acinar ventilation heterogeneity (Sacin) when switching patients from DPI-BUD to HFA-BDP_(1/1) and HFA-BDP_(1/2). Solid and open symbols refer to values (means ± SEMs) before and after bronchodilation at each visit. Solid and dotted lines correspond to patients with a baseline Sacin value above 0.12 L⁻¹ (abnormal Sacin subgroup) and below 0.12 L⁻¹ (normal Sacin subgroup), respectively; *P* values (ANOVA) are indicated whenever *P* < .05. **B,** Conductive ventilation heterogeneity (Scond) when switching patients from DPI-BUD to HFA-BDP_(1/1) and HFA-BDP_(1/2). Same representation as A.

TABLE II. Characteristics of 2 asthma subgroups with normal and abnormal acinar ventilation heterogeneity and effect of switching from DPI-BUD to HFA-BDP[‡]

	Normal Sacin (n = 14)			Abnormal Sacin (n = 16)			P value between 2 Sacin groups (DPI-BUD)
Sex distribution	8 male/6 female			11 male/5 female			
Age (y)	33 ± 3			57 ± 4			<.001
BUD dose	314 ± 46			413 ± 53			>.1
AQLQ score	5.81 ± 0.16			5.57 ± 0.21			>.1
	DPI-BUD	HFA-BDP _(1/1)	HFA-BDP _(1/2)	DPI-BUD	HFA-BDP _(1/1)	HFA-BDP _(1/2)	
FEV ₁ (%pred)	90 ± 4	90 ± 3	89 ± 4	62 ± 5	65 ± 4	66 ± 5	<.001
FEF ₇₅ (%pred)	59 ± 6	62 ± 6	58 ± 7	23 ± 3	24 ± 3	23 ± 4	<.001
FEF ₂₅₋₇₅ (%pred)	66 ± 6	67 ± 5	64 ± 6	30 ± 5	31 ± 5	30 ± 6	<.001
DLco (%pred)	97 ± 5	92 ± 4	95 ± 5	87 ± 4	92 ± 3	94 ± 4	>.1
sGaw (L/s/cmH ₂ O/L)	0.098 ± 0.013	0.108 ± 0.013	0.097 ± 0.013	0.061 ± 0.012	0.060 ± 0.011	0.060 ± 0.009	.040
RV _{pl} (mL)	1951 ± 164	1875 ± 195	1992 ± 214	3112 ± 280	2957 ± 283	2645 ± 227*	.002
FRC _{pl} (mL)	3251 ± 190	3101 ± 202	3290 ± 207	4153 ± 388	3987 ± 362	3909 ± 332	.051
TLC _{pl} (mL)	6123 ± 318	6079 ± 345	6139 ± 357	6397 ± 384	6241 ± 390	6299 ± 369	>.1
Sacin (L ⁻¹)	0.078 ± 0.007	0.084 ± 0.006	0.079 ± 0.008	0.270 ± 0.040	0.220 ± 0.031*	0.212 ± 0.029†	<.001
Scond (L ⁻¹)	0.058 ± 0.007	0.051 ± 0.008	0.055 ± 0.009	0.071 ± 0.006	0.074 ± 0.007	0.076 ± 0.006	>.1
FRC _{mbw} (mL)	3089 ± 221	3103 ± 306	2997 ± 230	3374 ± 246	3293 ± 232	3355 ± 261	>.1

[‡]DPI-BUD, after 6 weeks of budesonide dry powder inhaler; HFA-BDP_(1/1), after 6 weeks of ultrafine beclomethasone at equivalent dose; HFA-BDP_(1/2), after another 6 weeks of ultrafine beclomethasone at half dose. Same lung function and ventilation heterogeneity parameters as in Table I. Data shown are averages ± SEMs; significant changes from DPI-BUD: **P* < .05; †*P* < .01.

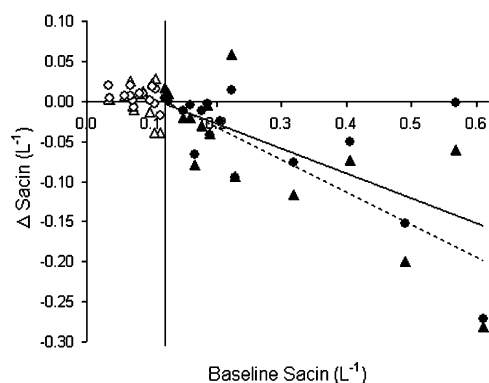


FIG 3. Change in acinar ventilation heterogeneity (Δ Sacin) versus baseline Sacin value at DPI-BUD. Open and solid symbols refer to patients with normal and abnormal baseline Sacin values, respectively (0.12 L^{-1} line indicates Sacin abnormality). Circles and triangles refer to Δ Sacin after HFA-BDP_(1/1) and HFA-BDP_(1/2), respectively. Regression lines of significant correlations within the abnormal Sacin subgroup (solid symbols) are also shown for HFA-BDP_(1/1) (solid line) and HFA-BDP_(1/2) (dotted line).

triangles and dotted line for abnormal Sacin subgroup correlation; $R = -0.76$; $P = .001$). As expected, the correlations between Δ Sacin and baseline Sacin were even more significant ($P < .001$ for all) when considering the entire group ($n = 30$, ie, including also the open symbols of Fig 3). Finally, it is interesting to note that except for 1 patient corresponding to a positive Δ Sacin value and a Sacin value at baseline of $\sim 0.23 \text{ L}^{-1}$, all patients who decreased Sacin after the first 6 weeks of HFA-BDP (solid circles) further decreased Sacin after another 6 weeks of HFA-

BDP even at half dose (solid triangles). In particular, 1 patient with Sacin at baseline of $\sim 0.57 \text{ L}^{-1}$, who did not improve Sacin after the first 6 weeks, did so in the 6 subsequent weeks.

DISCUSSION

This study shows that a functional improvement of acinar lung zone abnormality can be elicited in patients with otherwise well controlled asthma by delivering BDP as an ultrafine steroid aerosol formulation. The improvement in acinar ventilation heterogeneity, corresponding to a decrease in Sacin after switching the patients to HFA-BDP (Fig 2), was in fact correlated to the initial Sacin value measured when the patients were still on DPI-BUD (Fig 3). In particular, patients with no initial Sacin abnormality (generally corresponding to the patients with mildest asthma in terms of FEV₁; Table II) showed no changes in any of the lung function or ventilation distribution variables under study. This study is the first to quantify functional abnormality in the target lung zone of ultrafine steroid aerosols and to identify those patients with asthma who can really benefit from the ultrafine inhaled steroid. In our particular group of patients with asthma, the subgroup with initial Sacin abnormality showed a 25% decrease (ie, improvement) of Sacin abnormality after only 6 weeks of HFA-BDP.

In the current study, the switch from DPI-BUD to the ultrafine HFA-BDP was performed by first considering the same BDP dose and then only half that dose, despite previous studies showing equivalence of HFA-BDP to only half the DPI-BUD dose.^{6,7} Even when assuming that

the use of each device is optimal in study populations that are being compared, the equivalence factor for dosing between any 2 formulations will depend on the study parameter used. For instance, Busse et al¹⁶ have shown a 2.6 or 3.2 dosing factor between HFA-BDP and CFC-BDP depending on whether FEV₁ and/or FEF₂₅₋₇₅ was used to compare the dose-response curves. Also, this outcome might have been different if the use of spacers had been allowed. Considering also that in the current study average BUD dose was only 367 µg, the safest and most straightforward switch was that between 2 formulations of the same nominal steroid dose (DPI-BUD and HFA-BDP_(1/1)), followed by a switch to halve the BDP dose (HFA-BDP_(1/2)). In this way, aerosol deposition patterns for DPI-BUD and HFA-BDP_(1/1) differed solely as a result of the device-dependent particle size distributions. Because we merely sought to identify in which patients an acinar response could be elicited at all, dose was not a critical issue, but we could not exclude that the Sacin response could have been missed by halving the dose straight away. Clearly, Fig 2, A, shows that the acinar compartment does not respond to half or double the HFA-BDP dose in patients with asthma with normal Sacin. Although the HFA-BDP_(1/2) data in the abnormal Sacin subgroup indicate that the beneficial effect in responsive patients is maintained at half dose, this could still represent a carry-over effect from the 6-week episode at full dose, and only a dedicated dose-response study can answer the question of equivalence.

The subjects in the subgroup with the abnormal acinar heterogeneity were considerably older than the patients with normal Sacin. Taken together with previous studies,^{20,21} mean Sacin was 0.08 L⁻¹ (n = 14; Table II), 0.10 L⁻¹ (n = 13),²⁰ 0.20 L⁻¹ (n = 20),²¹ and 0.27 L⁻¹ (n = 16; Table II) in patients with asthma with a mean age of 33, 34, 39, and 57 years, respectively, suggesting a tendency of a worsening Sacin with age. Surely, the onset of asthma disease needs to be taken into account to explore further this intriguing effect of age, which is beyond the scope of this study. The patients with asthma with Sacin abnormality at baseline—that is, the subgroup benefiting from the ultrafine steroid aerosol formulation—typically had smaller FEV₁, lower end-expiratory flows, greater RV_{pl}, and a borderline greater FRC_{pl} in the face of a similar ventilated FRC_{mbw} (Table II). Plethysmographic measurements of thoracic gas volume have been shown to correlate better with distal lung inflammation than FEF₂₅₋₇₅ in patients with asthma.²⁴ In the current study, hyperinflation reflected in RV_{pl} decreased, whereas neither FEF₂₅₋₇₅ nor FEF₇₅ showed any improvements after switching to the ultrafine steroid aerosol in the abnormal Sacin subgroup. The absence of FEF₂₅₋₇₅ change seen here when switching from DPI-BUD to HFA-BDP at full or half dose agrees with previous reports of similar FEF₂₅₋₇₅ improvements in asymptomatic patients after either DPI-BUD or HFA-BDP at half dose.^{6,15}

The improved functionality of the acinar lung zone was accompanied by significant but mild changes in FEV₁, which is the parameter that is most frequently used to

assess the status of patients with asthma when comparing efficacy of inhaled drugs.^{6,7,9,10-12} Several of these previous reports have studied patients with poorly controlled asthma (usually undertreated in terms of steroid dose) before switching them to either ultrafine HFA-BDP or a coarser inhaled steroid aerosol.^{6,7,9,10,12} Also, studies comparing HFA-BDP with CFC-BDP did not use the latter with any spacers or holding chambers.^{9,11} Under such suboptimal conditions regarding steroid dosage and/or lung targeting at baseline, any subsequent enhancement in the inhaled steroid delivery was indeed expected to promote a patient's FEV₁. In the current study, we insisted on enrolling patients with asthma who had already been carefully titrated to the appropriate dose of inhaled steroids¹ (unsurprisingly therefore, AQLQ scores were good) and who were able to generate sufficient inspiratory flow to maximize peripheral deposition with the DPI.²⁵ Finally, we included only never-smoker patients with asthma for this study to avoid any confounding effects from the smoking-related alterations in conductive and acinar lung zones that can appear from as little as 10 pack-years onward.²² It was under these optimal conditions that the patients with asthma were assessed for their baseline acinar lung zone condition and their potential improvement on switching to a smaller particle steroid aerosol.

Interestingly, the abnormal Scond (>0.042 L⁻¹), which was present in all patients on entry into the study, remained unaffected by any change in inhaled steroid delivery. Given that particle sizes generated by breath actuated DPI-BUD are reported to range 2 to 6 µm (MMAD) depending on inhaled flow,²⁶ we had expected that some larger airways previously benefiting from the coarser DPI-BUD particles might have a functional deterioration when switching to HFA-BDP. This appears not to be the case, as can be best appreciated from the FEV₁ data in the normal Sacin subgroup (Table II), in which no acinar airways abnormality interferes that could mask a conductive airways effect on cumulative variables such as FEV₁. In addition, neither the spirometric indices of small conductive airway function (FEF₇₅ or FEF₂₅₋₇₅) nor sGaw (which probably reflects somewhat larger conductive airways) were affected by the switch to HFA-BDP.

The absence of deterioration in the conductive airways function when removing the coarser particles from the anti-inflammatory aerosol is probably related to the fact that the 1-µm to 2-µm particles in the overlapping size range of DPI-BUD and HFA-BDP aerosols are the ones producing the therapeutic effect on these airways proximal to the acinar entrance. The particles around 2 µm are expected to target predominantly the conductive airways, whereas the particles closer to 1 µm are able to reach the acinar zone. Yet a considerable portion of the latter particles is expected also to deposit by inertial impaction and gravitational sedimentation along the conductive airways on their passage to the acinar zone. In that sense, the switch from DPI-BUD to HFA-BDP will have mainly constituted a boost in the particle size range around 1 µm, where the upper size range (up to ~2 µm) maintains the conductive airways well controlled, whereas the lower

size limit (1 μm and below) increases its efficacy in the acinar airway compartment. The switch from DPI-BUD to full dose HFA-BDP_(1/1) may have exaggerated the boost in the aerosol size range directed at the conducting airways. However, the absence of any Scond change between HFA-BDP_(1/1) and HFA-BDP_(1/2) suggests that in this dose range, dose did not play a critical role.

We conclude that to assess the efficacy of inhalation drug targeting, it is imperative that the target zone be adequately monitored. In this particular study, we used ventilation heterogeneity to monitor the acinar lung zone, enabling us to identify the stable patient with asthma who can benefit from a steroid aerosol with a MMAD of $\sim 1 \mu\text{m}$. In general terms, the patients with the greater acinar lung zone abnormality, showing marked functional improvements, were those with the lower FEV₁ and were generally older. None of the patients, including those without acinar airways abnormality, showed any change their conductive airways abnormality when switching from a standard dry powder steroid to a steroid aerosol with a MMAD of $\sim 1 \mu\text{m}$.

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