The role of the small airways in the clinical expression of asthma in adults

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Background: The clinical relevance of increased ventilation heterogeneity, a marker of small-airways disease, in asthmatic patients is unclear. Ventilation heterogeneity is an independent determinant of airway hyperresponsiveness (AHR), improves with bronchodilators and inhaled corticosteroids (ICSs), and worsens during exacerbations, but its relationship to asthma control is unknown.

Objective: We sought to determine the association between ventilation heterogeneity and current asthma control before and after ICS treatment.

Methods: Adult subjects with asthma had lung function and asthma control (5-item Asthma Control Questionnaire [ACQ-5 score] ≥1.5 = poorly controlled, ACQ-5 score ≤0.75 = well controlled) measured at baseline. A subgroup with AHR had repeat measurements after 3 months of high-dose ICS treatment. The indices of ventilation heterogeneity in the regions of the lung where gas transport occurs predominantly through convection (ventilation heterogeneity in convection-dependent airways [Scond]) and through diffusion (ventilation heterogeneity in diffusion-dependent airways [Sacin]) were derived by using the multiple-breath nitrogen washout technique.

Results: At baseline (n = 105), subjects with poorly controlled asthma had worse FEV_1, fraction of exhaled nitric oxide measured at 200 mL/s (FENO), Scond, and Sacin values. In the treatment group (n = 50) spirometric, FENO, residual volume (RV)/total lung capacity (TLC), AHR, and Scond values significantly improved. Asthma control also improved (mean ACQ-5 score, 1.3-0.7; $P < .0001$). The change in ACQ-5 score correlated with changes in FENO ($r_s = 0.31$, $P = .03$), Sacin ($r_s = 0.32$, $P = .02$), and Scond ($r_s = 0.41$, $P = .003$) values. The independent predictors of a change in asthma control were changes in Scond and Sacin values (model $r^2 = 0.20$, $P = .005$).

Conclusions: Current asthma control is associated with markers of small-airways disease. Improvements in ventilation heterogeneity with anti-inflammatory therapy are associated with improvements in symptoms. Sensitive measures of small-airway function might be useful in monitoring the response to therapy in asthmatic subjects. (J Allergy Clin Immunol 2012;129:381-7.)

Key words: *Ventilation heterogeneity, small airways, asthma control, symptoms, inflammation, asthma, adults*

The clinical relevance of small-airways disease in subjects with stable asthma is unclear. The small airways are pathologically abnormal in subjects with both mild and severe disease.[1,2] Furthermore, inflammation in the small airways is more pronounced in patients with nocturnal asthma.[3] The physiologic consequences of abnormal small-airway function, such as airway closure,[4] have been associated with asthma exacerbations. To date, however, the relationship between asthma symptoms in subjects with stable disease and abnormal small-airway function has been largely unexplored. Understanding the role of the small airways in the manifestation of day-to-day symptoms and the effect of inhaled corticosteroid (ICS) treatment on this relationship could have implications for the development of therapies that specifically target the small airways and might lead to improved patient outcomes.

Increasing unevenness of ventilation between different lung regions (ventilation heterogeneity) is a sensitive marker of abnormal small-airway function and can be measured noninvasively by using the single-breath washout[5] or multiple-breath washout[6,7] techniques. These tests are able to quantify the degree of uneven ventilation in the distal airways by measuring the concentration of a tracer gas, such as nitrogen, at the mouth. Furthermore, small-airways disease can be compartmentalized by using the multiple-breath nitrogen washout (MBNW) technique to conducting airways, where gas transport occurs along pressure gradients by means of convection, and more peripheral airways, where gas transport occurs along concentration gradients by means of diffusion. The multiple-breath washout technique has been used to monitor early disease in subjects with cystic fibrosis[8] and in smokers with normal spirometric values[9] and to detect bronchiolitis after bone marrow transplantation.[10] Indices of ventilation heterogeneity improve after inhalation of bronchodilators[11] and treatment with ICSs.[12,13] Furthermore, ventilation heterogeneity worsens during a bronchial provocation test[14] and is an independent determinant of airway hyperresponsiveness (AHR) in asthmatic subjects.[13] Worsening ventilation heterogeneity as a feature of small-airway dysfunction has been reported in subjects with severe

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Abbreviations used
ACQ-5: 5-Item Asthma Control Questionnaire
AHR: Airway hyperresponsiveness
BDP-HFA: Beclomethasone dipropionate–hydrofluoroalkane
BMI: Body mass index
FENO: Fraction of exhaled nitric oxide measured at 200 mL/s
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
MBNW: Multiple-breath nitrogen washout
RV: Residual volume
Sacin: Ventilation heterogeneity in diffusion-dependent airways
Scond: Ventilation heterogeneity in convection-dependent airways
TLC: Total lung capacity

asthma exacerbations and remains abnormal after symptoms begin to resolve.[15] A previous study also reported worse ventilation heterogeneity by using the single-breath washout technique in patients with poorly controlled asthma.[16] These findings suggest that ventilation heterogeneity relates to features of asthma, such as AHR and variable airway function, and hence might have an important role in the clinical expression of the disease.

Clinical guidelines highlight the importance of assessing current asthma control.[17] This assessment should be based on the patient's symptoms, as well as lung function.[18] However, the latter is frequently omitted in clinical practice,[19] and the assessment of asthma control is increasingly reliant on symptom-based composite scores.[20,21] Spirometry is the most frequently used measure of airway function, yet it correlates weakly with asthma symptoms.[22] This suggests that other pathophysiologic abnormalities that are not detected by measuring FEV_1 might also contribute to asthma symptoms. Failure to recognize the full range of physiologic abnormality that is contributing to asthma symptoms might lead to the false conclusion that symptoms are related to nonasthma factors, such as obesity, unfitness, or even placebo effects.[23] Because treatment decisions are based on the assessment of asthma control, there is a need to better understand the physiologic correlates of asthma control, particularly symptoms.

We hypothesized that small-airways disease contributes to the clinical expression of chronic asthma. Our aims were to assess the relationship between ventilation heterogeneity and current asthma symptom control and to determine whether it correlates with the change in asthma control after treatment with high-dose ICSs.

METHODS

Adult subjects were recruited from a volunteer database at the Woolcock Institute of Medical Research by advertising throughout the University of Sydney and from referrals by local respiratory physicians. Subjects were eligible if they had a physician's diagnosis of asthma and either current symptoms, a current asthma prescription, or both.[24] Subjects were nonsmokers (<10 pack-year smoking history and no smoking within the last 6 months), had no chest infections or antibiotic or oral prednisone use in the previous 4 weeks, and had no lung disease other than asthma. Written informed consent was obtained from all subjects. The experimental protocol was approved by the Northern Sydney Central Coast Area Health Service and South West Sydney Area Health Service Human Research Ethics Committees, and the study is registered with the Australian and New Zealand Clinical Trials Registry.

Study design

The current dataset is a nonoverlapping analysis of prospectively collected data, as described below, from 33 of the 49 subjects recruited for 2 previously published treatment studies.[13,25] The remaining 16 subjects were not included in the current analysis because they lacked measurements of ventilation heterogeneity. The 3 studies had similar study designs and inclusion and exclusion criteria. All subjects attended the laboratory at baseline for assessment of asthma control and detailed lung function testing.

The treatment subgroup was composed of subjects with AHR and recent asthma symptoms who were willing to undergo treatment with high doses of ICSs for 8 to 12 weeks. AHR at baseline was chosen as a selection criterion because it indicates the presence of persisting abnormal airway function that would justify the intervention and should lead to a measurable change in the physiologic variables of interest. A sample size calculation indicated that 50 subjects in the treatment subgroup were needed for an anticipated correlation coefficient of 0.4 with a power of 0.8 and α value of .05. In the current study subjects doubled their ICS doses, and steroid-naive subjects were started on ICSs at 500 μg/d beclomethasone dipropionate–hydrofluoroalkane (BDP-HFA) equivalent.[26] In one of the published studies,[13] 20 subjects were treated with an ICS dose of 750 μg/d BDP-HFA equivalent, and in the second study[25] 13 subjects were treated with an ICS dose of 1000 μg/d BDP-HFA equivalent.

At each visit, subjects had the following measurements: Asthma Control Questionnaire (ACQ) score, fraction of exhaled nitric oxide measured at 200 mL/s (FENO) as a marker of inflammation, MBNW to measure ventilation heterogeneity, spirometry, plethysmography, and a bronchial provocation test to determine AHR. Atopic status was determined based on results of skin prick testing to a panel of common aeroallergens. Subjects withheld ICSs and long-acting β_2-agonists (LABAs) for 24 hours and short-acting β_2-agonists for 6 hours before each visit.

Asthma control

Asthma control was measured by using the short version symptom-only ACQ-5,[20,27] which allowed us to include spirometric parameters as independent variables in the analysis. Asthma control categories were defined as well controlled (ACQ-5 score $\leq$0.75), partly controlled (ACQ-5 score >0.75 but <1.5), and poorly controlled (ACQ-5 score $\geq$1.5).[28] A change in ACQ-5 score of greater than 0.5 was considered clinically important.[20]

FENO

FENO was measured by using a standard offline technique according to American Thoracic Society/European Respiratory Society guidelines[29] at a constant flow of 200 mL $\cdot$ s^{-1}, with the normal range defined as less than 13.0 ppb.[30]

MBNW

Ventilation heterogeneity was measured by using the MBNW, as previously described.[13] Briefly, a closed-circuit, bag-in-box breathing system was used to deliver 100% oxygen, which subjects breathed at a tidal volume of 1.0 to 1.3 L until the end-tidal nitrogen concentration decreased to one fortieth of the starting alveolar nitrogen concentration. The indices of ventilation heterogeneity in the peripheral regions of the lung, where gas transport occurs predominantly across a pressure gradient through convection (ventilation heterogeneity in convection-dependent airways [Scond]) and across a concentration gradient through diffusion (ventilation heterogeneity in diffusion-dependent airways [Sacin]), were derived.[11] The upper limit of normal for Scond is 0.037 L^{-1}, and that for Sacin is 0.130 L^{-1}.[13] The reproducibility for the same parameters are $\pm$0.026 L^{-1} for Scond and $\pm$0.027 L^{-1} for Sacin.[13]

Spirometry and plethysmography

Spirometry and whole-body plethysmography were performed according to American Thoracic Society/European Respiratory Society guidelines[31,32] by using a Medisoft BodyBox 5500 (Medisoft Corp, Sorrines, Belgium) and in 20 subjects by using an Autobox 6200 DL plethysmograph (Sensormedics Corp, Yorba Linda, Calif). Predicted values were derived according to published reference equations.[33,34]

TABLE I. Baseline demographics and lung function in 105 subjects with asthma at baseline

	Well controlled	Partly controlled	Poorly controlled	*P* value
No.	43	35	27	—
Sex (M/F)	24/19	11/24	7/20	.02
Age (y)	38 (34-42)	36 (32-40)	35 (30-40)	.60
Disease duration (y)	22 (18-25)	27 (23-32)	26 (22-31)	.08
BMI ($kg \cdot m^{-2}$)	26.0 (24.8-27.2)	26.1 (24.0-28.2)	27.7 (25.4-30.0)	.53
ICS use, no. (%)	32 (74)	28 (80)	19 (70)	.73
BDP-HFA (μg/d)	532 (423-641)	412 (305-520)	421 (328-514)	.18
LABA use (%)	72	63	70	.66
ACQ-5 score	0.3 (0.2-0.4)	1.1 (1.0-1.2)	2.0 (1.9-2.2)	—
FEV_1 (% predicted)	83 (78-88)	80 (75-85)	73 (66-80)*	.04
FVC (% predicted)	99 (95-103)	95 (90-100)	92 (86-99)	.17
FEV_1/FVC ratio (% predicted)	80 (76-84)	82 (78-86)	77 (72-83)	.33
FRC (% predicted)	115 (109-122)	118 (108-127)	118 (106-129)	.90
RV (% predicted)	133 (125-142)	141 (130-152)	144 (127-162)	.37
TLC (% predicted)	111 (107-115)	111 (106-116)	110 (104-115)	.94
RV/TLC ratio (% predicted)	122 (115-126)	130 (122-138)	133 (123-145)	.10
AHR positive (%)	70	80	89	.16
FENO (ppb)†	8.9 (7.4-10.7)	11.7 (9.8-14.5)*	13.2 (10.2-17.0)*	.02
Sacin (L^{-1})	0.118 (0.096-0.141)	0.114 (0.095-0.132)	0.156 (0.119-0.192)*	.05
Scond (L^{-1})	0.042 (0.035-0.049)	0.053 (0.043-0.063)	0.063 (0.047-0.079)*	.02

Data are presented as means (95% CIs), unless otherwise indicated. *P* values use ANOVA for continuous variables and the χ^2 test for categorical variables.
F, Female; *FRC*, functional residual capacity; *M*, male.
*Significant difference from the group with well-controlled asthma.
†Geometric mean (95% CI).

Bronchial provocation tests

The presence of AHR was determined by using a mannitol ($PD_{15}FEV_1 \leq 635$ mg mannitol[35]) or methacholine ($PD_{20}FEV_1 \leq 6.1$ μmol methacholine[36]) provocation test.

Statistical analysis

Statistical analysis was carried out with SAS version 9.2 software (SAS Institute, Inc, Cary, NC). FENO data were log-normally distributed and were log_{10} transformed for all analyses. ANOVA was used to determine differences in variables at baseline across the 3 asthma control categories. The χ^2 test was used for categorical variables. The paired *t* test was used to determine the effect of treatment compared with baseline for each outcome variable. The change in the ACQ-5 score during treatment (ΔACQ-5) was calculated as the ACQ-5 score after treatment minus the ACQ-5 score before treatment. A similar calculation was derived for the change in all dependent variables with the exception of ΔFENO, which was calculated as the percentage change with treatment. Univariate correlations were assessed by using Spearman correlation coefficients. The independent predictors of ACQ-5 (before treatment, after treatment, and ΔACQ-5) were identified by using forward stepwise multiple linear regressions with a model entry threshold at a *P* value of less than .2. The linear regressions were considered valid if the model was statistically significant ($P < .05$) and the residuals were normally distributed. Covariates included age, sex, height, weight, disease duration, smoking history, LABA use, ICS dose, FEV_1, forced vital capacity (FVC), FEV_1/FVC ratio, functional residual capacity, RV, TLC, RV/TLC ratio, FENO, AHR status, Scond, and Sacin. In each instance the regressions were repeated with the inclusion of body mass index (BMI) instead of height and weight to examine the effect of BMI as a clinically relevant variable on ACQ-5 scores. Data are expressed as means ± 95% CIs, unless otherwise indicated. Statistical significance was accepted at a *P* value of less than .05.

RESULTS

Baseline

Baseline demographics for 105 asthmatic subjects categorized according to current asthma control are shown in Table I. Subjects in this cohort were relatively young adults (range, 24-51 years), and there were no differences in age or disease duration across asthma control categories. Treatment intensities with ICSs and LABAs were similar between the groups. The prevalence of atopy (n = 98/105) and smoking history (mean, 0.6 pack years) did not differ between the groups.

Compared with the group with well-controlled asthma, subjects with poor asthma control were more likely to be female ($P = .02$) and had worse percent predicted FEV_1 ($P = .04$) and higher FENO ($P = .02$), Sacin ($P = .05$), and Scond ($P = .02$) values. Lung volumes and the prevalence of AHR were similar between groups.

Asthma control scores correlated with FEV_1, FENO, and Scond values, and there was a trend for a relationship with Sacin values (Table II). However, in the linear regression the independent predictors of ACQ-5 scores were FEV_1, FENO, age, and disease duration ($r^2 = 0.25$, $P < .0001$, Table III).

Treatment group

Fifty subjects underwent treatment with high-dose ICSs. Subjects in the treatment subgroup had evidence of suboptimal asthma control, poor lung function, and airway inflammation. Treatment significantly improved ACQ-5 scores, spirometric results, and FENO, RV/TLC ratio, and Scond values (Table IV). The mean improvement in ACQ-5 score of 0.6 ($P < .0001$) was clinically significant. After treatment, FEV_1 improved by 7% ($P < .0001$), and FENO values were reduced by 32% ($P < .0001$). All subjects had AHR before treatment, but after treatment, 72% of subjects remained AHR positive. The mean Scond value was abnormal before treatment and improved ($P < .0001$) but did not normalize with treatment. The mean Sacin value was also abnormal before treatment but did not change with treatment ($P = .40$). The change in ACQ-5 score and the measured physiologic parameters were similar irrespective of the ICS formulation

TABLE II. Univariate correlations for ACQ-5 scores at baseline in 105 subjects with asthma

Variable	r_s Coefficient	*P* value
Age (y)	−0.08	.40
Disease duration (y)	0.15	.12
BMI (kg · m^{-2})	0.09	.36
FEV_1 (% predicted)	−0.22	.02
FVC (% predicted)	−0.19	.04
FEV_1/FVC ratio (% predicted)	−0.11	.28
FRC (% predicted)	0.08	.43
RV (% predicted)	0.09	.38
TLC (% predicted)	0.02	.81
RV/TLC ratio (% predicted)	0.16	.14
FENO (ppb)	0.27	.005
Sacin (L^{-1})	0.17	.09
Scond (L^{-1})	0.26	.008

TABLE III. Results of a forward stepwise multiple linear regression to identify the independent predictors of ACQ-5 scores in 105 subjects with asthma at baseline

Predictors of ACQ-5 scores at baseline in whole cohort	β-coefficient ± SE	Partial r^2	Model r^2	*P* value
FEV_1 (L)	−0.43 ± 0.10	0.094	—	—
FENO (ppb)	0.02 ± 0.008	0.084	—	—
Age (y)	−0.02 ± 0.007	0.033	—	—
Disease duration (y)	0.01 ± 0.006	0.034	0.247	<.0001

used during the study period, with the exception of a significantly greater improvement in percent predicted FVC in the subgroup that received fluticasone propionate (see Table E1 in this article's Online Repository at www.jacionline.org).

The change in ACQ-5 score after ICS treatment (ΔACQ-5) correlated with changes in FENO, Sacin, and Scond values (Table V). In the linear regression changes in Sacin and Scond values were the only independent predictors of ΔACQ-5 ($r^2 = 0.20$, $P = .005$, Table VI). Fig 1 illustrates the relationship between the change in ACQ-5 score and changes in Sacin and Scond values during the treatment period. The majority (11/14) of those subjects with an improvement in Sacin values of greater than $-0.027\ L^{-1}$ had a clinically significant improvement in ACQ-5 scores. Furthermore, Sacin values worsened in all subjects who had a clinically significant deterioration in the ACQ-5 score (ΔACQ-5 score >0.5). In the treatment subgroup, the ACQ-5 score at baseline was predicted by FEV_1, FENO, and ICS dose ($r^2 = 0.34$, $P = .0003$). After treatment, ACQ-5 scores correlated with BMI ($r_s = 0.29$, $P = .04$), percent predicted FEV_1 ($r_s = -0.36$, $P = .01$), and RV/TLC ratio ($r_s = 0.31$, $P = .02$).

DISCUSSION

In the current study ventilation heterogeneity was worse in patients with poorly controlled asthma. Furthermore, changes in ventilation heterogeneity after a period of ICS treatment correlated with changes in asthma symptom control independently of all other measured physiologic variables. These results demonstrate that abnormal small-airway function contributes to the expression of asthma symptoms.

The novel findings from this analysis advance our understanding of the underlying causes of asthma symptoms. The cross-sectional analysis of this reasonably large cohort showed that subjects with poorly controlled asthma had worse ventilation heterogeneity compared with well-controlled subjects. These results extend the findings of a previous study reporting an association between asthma control (7-item ACQ) and ventilation heterogeneity, as measured by using the single-breath washout technique.[16] However, it was unknown whether that relationship was due to the known correlation between ventilation heterogeneity and FEV_1[13] or because of an association between ventilation heterogeneity and asthma symptoms. A recent study has highlighted the disparity between changes in FEV_1 and changes in symptoms in response to bronchodilator therapy,[23] as well as the placebo effect on symptoms. Therefore the ACQ-5 score was chosen as the outcome variable to determine whether ventilation heterogeneity contributes to symptoms. Symptom-only measures of asthma control have been validated and used widely in clinical trials,[21,37] as well as in clinical practice,[19,38,39] but until now, little has been known about their physiologic correlates.

At baseline, the main independent predictors of asthma symptom control were airway caliber (FEV_1) and airway inflammation (FENO), which is consistent with previous studies.[40,41] Ventilation heterogeneity was not an independent predictor, despite being worse in subjects with poorly controlled asthma. However, FEV_1 correlated with both Sacin ($r_s = -0.51$, $P < .001$) and Scond ($r_s = -0.48$, $P < .001$) values at baseline, suggesting that common factors, which might include airway inflammation, airway remodeling, and lung elastic properties, contribute to both abnormalities in FEV_1 and ventilation heterogeneity.

Measures of ventilation heterogeneity were the only independent predictors, explaining 20% of the variance of a change in asthma control after ICS treatment. In the univariate analysis changes in asthma control correlated weakly to changes in both airway inflammation and ventilation heterogeneity but not to changes in airway caliber. However, the contribution of changes in small-airway function to changes in asthma control was independent of changes in airway inflammation. It is possible that the effect of ICSs on small-airway inflammation was incompletely captured by the measurement of FENO or that changes in noneosinophilic inflammation or noninflammatory changes in the small airways (eg, edema) account for the effect of ventilation heterogeneity on the change in asthma control. Clearly the determinants of patient-reported symptoms are complex and include both physiologic and nonphysiologic factors, and it is likely that the contribution of any individual physiologic parameter will be small.

The change in ventilation heterogeneity in the diffusion-dependent airways, based on Sacin values, correlated with the change in asthma symptom control and was the strongest independent predictor accounting for 13% of the measured variance in linear regression. However, Sacin values improved in some subjects but worsened in others, resulting in a nonsignificant change overall. Importantly, Sacin values worsened in all subjects who had a clinically significant deterioration in asthma control. The reasons for the clinical deterioration in some subjects despite high-dose ICSs might include poor adherence, which was not objectively monitored, or variability in asthma control between visits because of environmental or allergen

TABLE IV. Change in ACQ-5 scores and physiologic parameters in 50 subjects with asthma after treatment with ICSs

Variable	Before treatment	After treatment	Change*	*P* value
ACQ-5 score†	1.3 (1.1 to 1.5)	0.7 (0.5 to 0.9)	−0.6 (−0.9 to −0.4)	<.0001
FEV_1 (% predicted)	72 (68 to 76)	79 (75 to 83)	7 (4 to 9)	<.0001
FVC (% predicted)	89 (85 to 92)	95 (98 to 99)	6 (3 to 8)	<.0001
FEV_1/FVC ratio (% predicted)	79 (75 to 83)	82 (78 to 86)	3 (1 to 6)	.002
FRC (% predicted)	114 (106 to 123)	113 (104 to 121)	−2 (−6 to 3)	.11
RV (% predicted)	144 (134 to 154)	138 (127 to 149)	−6 (−14 to 2)	.12
TLC (% predicted)	108 (103 to 112)	108 (103 to 113)	1 (−1 to 2)	.48
RV/TLC ratio (% predicted)	135 (129 to 141)	129 (122 to 135)	−6 (−11 to −2)	.009
AHR positive (%)	100	72‡	28‡	—
F_{ENO} (ppb)§	13.4 (11.5 to 15.8)	7.9 (6.8 to 9.1)	−32 (−43 to −21)‖	<.0001
Sacin (L^{-1})	0.147 (0.125 to 0.169)	0.142 (0.121 to 0.163)	−0.005 (−0.017 to 0.007)	.40
Scond (L^{-1})	0.063 (0.054 to 0.071)	0.047 (0.039 to 0.055)	−0.016 (−0.022 to −0.009)	<.0001

Data are presented as means ± 95% CIs, unless otherwise indicated.
*The change in variables is calculated from the absolute difference, unless otherwise indicated.
†A negative change in ACQ score denotes an improvement in asthma control between visits.
‡N = 47.
§Geometric mean (95% CI).
‖Percentage change from baseline.

TABLE V. Univariate correlations for the change in ACQ-5 scores in 50 subjects with asthma after treatment with ICSs*

Variable†	r_s Coefficient	*P* value
FEV_1 (% predicted)	−0.16	.27
FVC (% predicted)	−0.07	.63
FEV_1/FVC ratio (% predicted)	−0.06	.66
FRC (% predicted)	−0.04	.76
RV (% predicted)	0.18	.22
TLC (% predicted)	0.24	.09
RV/TLC ratio (% predicted)	0.16	.28
F_{ENO} (ppb)‡	0.31	.03
Sacin (L^{-1})	0.32	.02
Scond (L^{-1})	0.41	.003

*The change in ACQ-5 score refers to ACQ-5 scores after treatment minus ACQ-5 scores before treatment, and a reduction in the ACQ-5 score represents an improvement in asthma control.
†Variables refer to the absolute change (after treatment minus before treatment), unless otherwise indicated.
‡Percentage change from baseline.

TABLE VI. Results of a forward stepwise multivariate linear regression to identify the independent predictors of changes in ACQ-5 scores with ICS treatment

Predictors of changes in ACQ-5 scores* with treatment	β-coefficient ± SE	Partial r^2	Model r^2	*P* value
Sacin (L^{-1})*	6.73 ± 3.05	0.13	—	—
Scond (L^{-1})*	11.35 ± 5.53	0.07	0.20	.005

All predictor variables remaining in the model are significant at a *P* value of less than .05.
*Variables refer to the absolute change from baseline (after treatment minus before treatment).

exposures. The improvement in Scond values after ICS treatment is consistent with previous studies,[12,13,42] but in this population, compared with changes in Sacin values, changes in Scond values accounted for proportionally less of the measured variance in the change in asthma symptom control. It is also noteworthy that changes in spirometric parameters were insensitive to the change in asthma symptom control despite significant improvements in FEV_1 and FEV_1/FVC ratios after ICS treatment. Persisting small-airway dysfunction might explain the clinical observation that some patients continue to experience suboptimal control despite high doses of ICSs.[43] These findings also suggest that therapeutics specifically targeting heterogeneity in the small airways could lead to improved patients' symptoms and outcomes.

The mechanisms by which small-airways disease leads to daily asthma symptoms remain unclear. A reduction in small-airway caliber increases the work of breathing because of the increased resistive load. In addition, a mild degree of ventilation heterogeneity in the periphery predisposes to even worse ventilation heterogeneity and airway closure when bronchoconstriction occurs.[44] The end result is a magnified increase in respiratory system stiffness,[45] which is a strong determinant of symptoms during bronchoconstriction in asthmatic subjects.[46] These mechanisms are consistent with the observations that airway closure[4] and air trapping[47] as physiologic manifestations of small-airways disease are associated with recurrent asthma exacerbations. Although air trapping measured by the RV/TLC ratio improved during the study and correlated with ACQ-5 scores after treatment, it was not an independent predictor of the change in asthma control after ICS treatment. The degree of ventilation heterogeneity is related to the amount of airway closure, but the relationship between changes in these parameters and asthma symptoms is complex because some subjects with significant improvement in ACQ-5 scores exhibited improvement in RV/TLC ratios but worsening in Sacin values. The worsening in ventilation heterogeneity in the distal airways after ICS treatment has been previously observed[12] and could occur if the improvement in airway closure results in the recruitment of poorly ventilated lung units.

A limitation of the current study is the underrepresentation of the severe asthma phenotype. Nevertheless, measuring ventilation heterogeneity might have clinical applicability in the management of difficult-to-treat asthma, and this requires further study, ideally in a larger treatment cohort. Although the current analysis combines data from 3 treatment studies, the methodology was similar, and in particular, all MBNW measurements were made on the same device. When the datasets were analyzed separately, the relationships were similar. In particular, there was a persistent lack

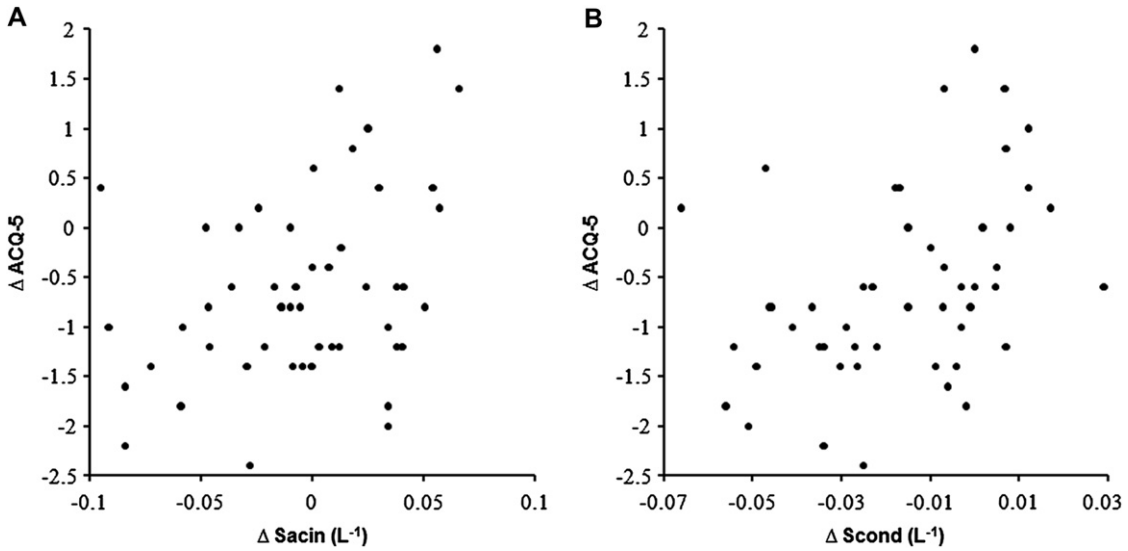


FIG 1. The change in asthma control after treatment with ICSs correlates with changes in Sacin values (univariate correlation using the Spearman test [r_s] = 0.32, P = .003; **A**) and changes in Scond values (r_s = 0.41, P = .005; **B**).

of any association between AHR to methacholine or mannitol measured as a continuous variable by using the dose-response slope and the change in asthma control after ICS treatment. Subjects in the treatment subgroup received high-dose ICSs by using different formulations, but the change in ventilation heterogeneity parameters was not statistically different between different ICS subgroups. The conversion to BDP-HFA equivalents is only approximate because of differences in deposition associated with different preparations. The small number of subjects in each subgroup precluded any definitive assessment about the effect of ultrafine ICS particle formulations on measures of small-airway function and its relationship to asthma symptom control. Future studies comparing large and ultrafine ICS particles should include such sensitive measures of small-airway function.

In summary, increased ventilation heterogeneity in the small airways is associated with poor asthma control. During a period of ICS treatment, the change in ventilation heterogeneity predicted the change in asthma symptom control independently of all other measured physiologic variables. Thus small-airway function is relevant to the clinical manifestation of chronic asthma. Therapies specifically targeting the small airways might improve outcomes in asthmatic subjects.

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Clinical implications: Small-airways disease in asthmatic subjects plays a role in the expression of symptoms. Therapies targeting abnormalities in the small airways might improve asthma outcomes.

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TABLE E1. Comparison of the change in physiologic parameters in a group of 50 subjects with asthma based on the ICS formulation used during the study

Variable#	BUD (n = 10)	BDP-CFC (n = 10)	BDP-HFA (n = 13)	FP (n = 17)	*P* value
ACQ-5 score*	−0.46 (−1.28 to 0.36)	−0.64 (−0.2 to −1.1)	−0.68 (0 to −1.35)	−0.66 (−1.11 to −0.21)	.95
FEV_1 (% predicted)	8.4 (3.2 to 13.6)	4.3 (0.1 to 8.4)	4.1 (−0.9 to 9.1)	9.6 (3.5 to 15.6)	.30
FVC (% predicted)	4.1 (1.4 to 6.8)	2.8 (−2.4 to 8.0)	0.4 (−3.3 to 4.1)	12.5 (8.0 to 17.0)†	.0001
FEV_1/FVC ratio (% predicted)	5.3 (0.1 to 10.5)	1.9 (−2.4 to 6.0)	4.0 (1.1 to 6.8)	3.5 (−2.6 to 9.6)	.83
FRC (% predicted)	−2.8 (−20.6 to 15.0)	−1.8 (−9.4 to 5.7)	−2.9 (−7.6 to 1.8)	−0.6 (−10.0 to 8.7)	.98
RV/TLC ratio (% predicted)	−7.5 (−20.1 to 5.1)	−4.6 (−19.0 to 9.9)	0.7 (−5.2 to 6.7)	−12.7 (−23.4 to 2.1)	.24
F_{ENO} (ppb)‡§	−23 (−46 to 1)	−16 (−56 to 24)	−45 (−61 to −28)	−37 (−53 to 22)	.23
Sacin (L^{-1})	−0.002 (−0.024 to 0.020)	−0.026 (−0.046 to 0.007)	−0.003 (−0.032 to 0.026)	0.004 (−0.020 to 0.028)	.31
Scond (L^{-1})	−0.014 (−0.035 to 0.007)	−0.020 (−0.037 to −0.003)	−0.020 (−0.032 to −0.009)	−0.011 (−0.022 to 0.000)	.63

Data are presented as means ± 95% CIs, unless otherwise indicated. *P* values were determined by using ANOVA.

BDP-CFC, Beclomethasone dipropionate–chlorofluorocarbon metered-dose inhaler; *BDP-HFA*, beclomethasone dipropionate–hydrofluoroalkane metered-dose inhaler; *BUD*, budesonide dry powder inhaler; *FP*, fluticasone propionate–hydrofluoroalkane metered-dose inhaler; *FRC*, functional residual capacity.

*A negative change in ACQ score denotes an improvement in asthma control between visits.

†Significantly different from other groups.

‡Geometric mean (95% CI).

§Percentage change from baseline.

#The change in variables is calculated as the absolute difference unless otherwise indicated.