

Peripheral lung function in patients with stable and unstable asthma

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Background: Exacerbations of asthma are thought to be caused by airflow obstruction resulting from airway inflammation, bronchospasm, and mucus plugging. Histologic evidence suggests the small airways, including acinar air spaces, are involved; however, this has not been corroborated *in vivo* by measurements of peripheral small-airway function.

Objective: We sought to determine whether asthma severity is linked to small-airway function, particularly in patients with acute severe asthma.

Methods: Eighteen subjects admitted for an asthma exacerbation underwent lung function testing, including measures of acinar ventilation heterogeneity (S_{acin}) and conductive ventilation heterogeneity (S_{cond}) using the multiple-breath nitrogen washout. Treatment requirement was defined according to Global Initiative for Asthma scores. Data were compared with those obtained in 19 patients with stable asthma. **Results:** For the asthma exacerbation group, the median FEV₁ was 59% of predicted value (95% CI, 45% to 75% of predicted value), the median S_{cond} value was 185% of predicted value (95% CI, 119% to 245% of predicted value), and the median S_{acin} value was 225% of predicted value (95% CI, 143% to

392% of predicted value). FEV₁ (percent predicted) was correlated with S_{acin} (percent predicted) values (Spearman $\rho = -0.67$, $P = .006$) but not with S_{cond} (percent predicted) values ($P > .1$). The Global Initiative for Asthma score was significantly related to S_{acin} (percent predicted) (Spearman $\rho = 0.59$, $P = .016$) but not to S_{cond} (percent predicted) values ($P > .1$). The unstable group was characterized by considerably lower forced vital capacity ($P < .001$) and higher S_{cond} ($P = .001$) values than the unstable group. In a subgroup of 11 unstable patients who could be reviewed after 4 weeks, FEV₁, forced vital capacity, S_{acin} , and S_{cond} values showed marked improvements.

Conclusion: Our findings suggest that unstable asthma is characterized by a combined abnormality in the acinar and conductive lung zones, both of which are partly reversible. Functional abnormality in the acinar lung zone in particular showed a direct correlation with airflow obstruction and treatment requirement in patients with acute severe asthma. (J Allergy Clin Immunol 2013;■■■■:■■■■-■■■■.)

Key words: Severe asthma, acinar airways, peripheral gas mixing

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Support for this study was provided by the Cooperative Research Centre for Asthma and Airways and the National Health and Medical Research Council, Australia.

Disclosure of potential conflict of interest: B. R. Thompson, M. J. Ellis, V. J. Kelly, R. E. O'Hehir, and S. Verbanck have received grants from the National Health and Medical Research Council and the Cooperative Research Centre for Asthma and Airways. J. A. Douglass has received grants from the National Health and Medical Research Council and the Cooperative Research Centre for Asthma and Airways; is on an advisory board for Novartis; has received payment for lectures from AstraZeneca, GlaxoSmithKline, and Novartis; and has received royalties from Health Press Limited. G. G. King has received grants from the National Health and Medical Research Council, GlaxoSmithKline, Boehringer Ingelheim, Pharmaxis, and the Asthma Foundation; has received travel support from GlaxoSmithKline, Novartis, AstraZeneca, Boehringer Ingelheim, and Pfizer; has received subject payments for clinical trials from Pharmaxis; and is part of a consultancy agreement between GlaxoSmithKline, Novartis, AstraZeneca, Boehringer Ingelheim, Pfizer, and the Woolcock Institute of Medical Research, and his research group receives an unrestricted allocation as part of the monies received from the consultancy agreements.

Received for publication October 8, 2012; revised January 22, 2013; accepted for publication January 24, 2013.

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http://dx.doi.org/10.1016/j.jaci.2013.01.054

The need to monitor small-airways function down to the acinus is increasingly being viewed as important in a number of respiratory conditions.¹ Exacerbations of asthma are thought to be caused by airflow obstruction resulting from airway inflammation, bronchospasm, and mucus plugging.²⁻⁴ Histologic evidence in asthmatic patients suggests that the small airways, including acinar air spaces, are involved.^{2,3} Increased airway heterogeneity that occurs in asthmatic patients also increases airway resistance^{5,6} and is therefore likely to contribute to airflow obstruction. Spirometric indices of small-airway obstruction, such as forced expiratory flow between 25% and 75% of forced vital capacity (FVC) or forced expiratory flow at 75% of FVC, are also seen to be reduced in asthmatic patients; however, there is clear evidence to suggest that these measures are not sensitive or specific to small-airway obstruction,⁷⁻⁹ especially in the presence of large-airway flow obstruction or gas trapping.

The multiple-breath nitrogen washout (MBW) test has been used to measure conducting ventilation heterogeneity (S_{cond}) and acinar ventilation heterogeneity (S_{acin}) zones in asthmatic patients.^{10,11} Increased ventilation heterogeneity has been demonstrated in the small conducting airways of asthmatic patients, even in adults with mild asthma¹¹ and children with asthma but normal interval spirometry.¹² Conductive airways ventilation heterogeneity has also been shown to be a strong predictor of airway hyperresponsiveness independent of airway inflammation.¹³ Furthermore, very recent studies have demonstrated correlates of MBW indices to asthma control.^{14,15}

Abbreviations used

ACQ: Asthma Control Questionnaire
 FRC: Functional residual capacity
 FVC: Forced vital capacity
 GINA: Global Initiative for Asthma
 MBW: Multiple-breath nitrogen washout
 S_{acin} : Acinar ventilation heterogeneity
 S_{cond} : Conductive ventilation heterogeneity
 Sn: Normalized slope of phase III from the nitrogen trace

Increased ventilation heterogeneity in the acinus has been present to varying degrees in a number of studies.^{10,11,13,16,17} Ventilation in the acinar zone in asthmatic patients responds to bronchodilator administration but does not normalize in all patients.^{11,13,18} Transbronchial biopsy studies in patients with severe asthma³ have demonstrated increased inflammation in the lung periphery involving the acinar air spaces that determine S_{acin} . In 2 inhaled corticosteroid treatment studies of asthmatic patients, S_{acin} values decreased.^{13,15} Treatment with a fine-particle corticosteroid aerosol further improves acinar heterogeneity if an abnormality persists after treatment with a larger-particle corticosteroid formulation.¹⁸ However, in all of these studies,^{13,15,18} S_{acin} values persisted even after patients' symptoms had become well-controlled based on asthma control questionnaires. In a recent study both S_{acin} and S_{cond} values correlated with asthma control measured by using the Asthma Control Questionnaire (ACQ),¹⁴ and furthermore, both indices also predicted the changes in ACQ scores when corticosteroid treatment was downtitrated or uptitrated.¹⁵ Importantly, it was the index of S_{acin} that predicted loss of treatment control. These results suggest that S_{acin} values might be an important determinant of asthma severity and loss of treatment control. Because these values respond to inhaled treatment, they might be an important zone that should be considered in the treatment of patients with severe or uncontrolled asthma.

It is unknown whether S_{acin} or S_{cond} values relate to airflow obstruction measured by spirometry in patients with stable asthma or during an asthma exacerbation. Previous reports show a lower average FEV₁ value for asthmatic patients with abnormal S_{acin} versus patients with normal S_{acin} ¹⁸ and a lower average FEV₁ and greater average S_{acin} value in asthmatic patients receiving maintenance treatment in excess of 500 μg of beclomethasone dipropionate equivalent versus patients receiving lower maintenance doses.¹⁷ Although previous studies have demonstrated that S_{acin} values do respond to treatment, acinar heterogeneity still persists after symptomatic control.^{14,15,18} Therefore we expect there to be a relationship between S_{acin} values and FEV₁ independent of whether the patient's asthma is stable or unstable. How S_{acin} and S_{cond} values relate to asthma severity as defined by the Global Initiative for Asthma (GINA) score is also unknown. Given the association between S_{acin} values and asthma control,¹⁵ there might also be an association with S_{acin} values and treatment requirement. Therefore we hypothesized that ventilation heterogeneity (both S_{acin} and S_{cond}) values are associated with airflow obstruction (spirometry) and treatment requirement (GINA step score). Our aims were to examine the relationship between measures of ventilation heterogeneity in the acinar and conductive zones and airway obstruction and treatment requirements, as measured by using GINA step scores.

METHODS**Subject selection: Asthma exacerbation group**

The study was approved by the Alfred Hospital Ethics Committee. Consecutive patients with a severe exacerbation of asthma were recruited on admission to the emergency department at the Alfred Hospital, Melbourne, Australia. Patients were included if their admission peak flow readings were less than 50% of their previously obtained personal best value and did not reach 80% or more of their personal best value after bronchodilator and corticosteroid treatment. Inclusion required a hospital length of stay of greater than 24 hours. The severity of asthma was defined by the patient's treatment requirements by using the medication step in the GINA guidelines. The GINA step was taken from each patient's maintenance asthma medications at the time of presentation to the emergency department.¹⁹ Patients with an abnormal chest radiograph were excluded. Within 48 hours after admission, all patients had measurements of spirometric and S_{acin} and S_{cond} values. All measurements were performed a minimum of 4 hours after short-acting bronchodilator therapy. No patients were receiving supplemental oxygen at the time of testing. All the patients with asthma exacerbations were discharged home on oral corticosteroids for between 3 and 5 days after discharge and were offered review. Eleven of the 18 patients enrolled had all their measurements repeated approximately 4 weeks after discharge.

Subject selection: Stable asthma

Patients with stable asthma were recruited from asthma outpatient clinics within the Alfred Hospital. Patients were included if they had reported no exacerbations or changes in symptoms/medication use for 6 weeks or less, if they had ACQ scores of less than 0.75,²⁰ and if they were current nonsmokers or exsmokers having not smoked for 6 months or more and with a smoking history of less than 5 pack years. Again the severity of asthma was defined by the patient's treatment requirements by using the medication step in the GINA guidelines at the time of measurement. Twelve of the 19 patients with stable asthma recruited have already been included in a recent publication.²¹

MBW test

Ventilation heterogeneity was estimated from the MBW test, as previously described.²⁰⁻²³ Briefly, the normalized slope of phase III from the nitrogen trace (Sn) after consecutive 100% oxygen breathing with a 1-L tidal volume from a stable functional residual capacity (FRC; respiratory rate, 10-12 breaths/min) is plotted against lung turnover. Based on MBW theory, the rate of increase in Sn versus turnover plot is a measure of S_{cond} proximal to the acinar entrance, whereas the offset of the entire Sn versus turnover plot reflects S_{acin} .²³ S_{cond} values were quantified by determining the rate of Sn increase with turnover beyond a turnover value of 1.5. The rate of Sn increase is then partially subtracted from the normalized slope of the first expiration to obtain S_{acin} values. All MBW measurements were performed before spirometry (Platinum series; Medigraphics, St Paul, Minn). Prediction equations were those of the National Health and Nutrition Examination Survey III²⁴ for spirometric results, Verbanck et al²⁵ for S_{acin} and S_{cond} values, and the European Community for Steel and Coal²⁶ for FRC values.

Statistical analysis

All analyses except multiple stepwise regression were performed with MedCalc (Mariakerke, Belgium). Relationships between continuous and categorical variables were explored by using Spearman rank correlations. Differences in the variables of interest between groups were examined with the Wilcoxon rank sum test and within-group changes with a Mann-Whitney *U* test. Multiple stepwise regression was performed with STATISTICA 5.5 software (StatSoft, Tulsa, Okla) to explore the relative contributions of S_{acin} and S_{cond} values to FEV₁ or FVC values, testing also for colinearity between S_{acin} and S_{cond} values. In all cases a 2-sided *P* value of .05 was used to indicate statistical significance.

RESULTS

Thirty-seven asthmatic patients were studied, including 18 patients admitted acutely to the hospital with an exacerbation of

asthma and 19 subjects with stable asthma. Demographics and pulmonary function data are shown in Table I. Even though the asthma exacerbation group had a peak expiratory flow of less than 50% of their personal best value at admission, there was some degree of recovery by the time the patients were tested in the laboratory (within 48 hours). The median peak expiratory flow value for the patients with an exacerbation of asthma was 73% of predicted value (95% CI, 56% to 87% of predicted value) at the time of MBW testing.

In the asthma exacerbation group there was a significant association of FEV₁ (percent predicted) with S_{acin} (percent predicted) values ($n = 18$, $\rho = -0.67$, $P = .006$) but not with S_{cond} (percent predicted) values ($P > .1$, Fig 1). The correlation between S_{acin} values and FEV₁ within the stable asthma group did not reach significance ($P = .06$), likely because of the relatively small range in FEV₁ in that cohort. However, Fig 1 (left panel) shows that the stable asthma S_{acin} data points (open circles) blend in with the unstable group in the overlapping FEV₁ range. In fact, in the combined group of patients with stable and unstable asthma, the correlation between S_{acin} values and FEV₁ was highly significant ($n = 37$, $\rho = -0.57$, $P < .001$).

We also explored the role of air trapping in the asthmatic groups under study, as previously done by Sorkness et al,²⁷ who compared FVC values between groups of asthmatic patients for a given degree of obstruction (in terms of FEV₁/FVC ratio). It can be seen from Table I that for a similar FEV₁/FVC ratio in the asthma exacerbation and stable asthma group, there was significantly more air trapping (ie, lower FVC percent predicted), lower FEV₁, and higher S_{cond} values in the patients with an exacerbation of asthma compared with those with stable asthma (Table I). Finally, the potential contributions of S_{acin} and S_{cond} values to either FEV₁ (Fig 1) or FVC (Fig 2) measurements were also examined by using multiple regression analysis in each asthma group and in the combined group (Table II). In all multiple regression analyses colinearity between S_{acin} and S_{cond} values was found to be negligible (tolerance of ≥ 0.84). FVC was associated with S_{cond} but not with S_{acin} values when considering all asthmatic patients ($n = 37$) but neither S_{cond} nor S_{acin} values were retained as a significant contributor to FVC in each asthma group separately. For FEV₁, the S_{acin} value was retained as the sole contributor in all groups studied, confirming the above result from the Spearman rank correlations.

In the asthma exacerbation group there was a significant relationship of GINA scores with S_{acin} (percent predicted) values ($\rho = 0.59$, $P = .016$; Fig 3, left panel) but not with S_{cond} (percent predicted) values ($P > .1$; Fig 3, right panel). There was a significant spread in percent predicted S_{acin} values for the 3 patients who are in step 5 of the GINA score; the relationship between S_{acin} values and GINA scores was maintained, even when these 3 patients were removed from the regression analysis ($\rho = 0.71$, $P = .008$). Because the patients with stable asthma had GINA step levels of either 3 or 4, regression analysis was not performed in this group.

In the subgroup of patients with asthma exacerbations who could be studied at the return visit (11/18), there were significant improvements between in-patient and return visit measurements of FEV₁ (percent predicted), FVC (percent predicted), S_{acin}, and S_{cond} values; there was no statistically significant change in FEV₁/FVC ratio or FRC (percent predicted) values (Table I). Individual values for FEV₁, FVC, S_{acin}, and S_{cond} while the patient was an inpatient and during the subsequent review are shown in Fig 4

and compared with the 95% CI range for these parameters obtained in the group with stable asthma. Although 2 of 11 patients had S_{acin} values that remained greater than the upper limit of normal, all patients had S_{cond} values of less than the upper limit of normal after treatment (Table I). Finally, there were no significant correlations between changes in FEV₁ or FVC values and changes in S_{acin} or S_{cond} values ($P > .1$ for all).

DISCUSSION

The most important finding of the present study is the association of FEV₁ with S_{acin} values but not with S_{cond} values within cohorts of patients with an exacerbation of asthma and stable asthma. These data confirm our hypothesis that the function of the acinus is an important determinant of FEV₁ in asthmatic patients. In the patients with an asthma exacerbation, there was also an association between S_{acin} values and GINA step scores. There was no association between S_{cond} values and FEV₁ or treatment requirements. The finding that a major determinant of airflow obstruction, as determined by the association between S_{acin} values and FEV₁ in asthmatic patients, is located within the acinar zone defines an important additional target for therapy. This could imply alternative drugs or alternative mechanical methods to get the drugs to the peripheral lung zone (eg, new aerosol modalities, intravenous, or oral delivery).

Although measurement of lung function is one determinant of asthma severity, airway obstruction is not strongly associated with either the frequency or severity of asthma symptoms or the occurrence of asthma exacerbations. Hence asthma severity in clinical practice is assessed by the amount of treatment required to maintain asthma control.²⁸ In the asthma exacerbation group GINA scores were related to S_{acin} values, and although the GINA score at the time of presentation might not be an adequate representation of true asthma severity (ie, the GINA score in this situation underestimates the actual level of severity), the significant correlation of GINA scores with S_{acin} values demonstrates the importance of the peripheral lung zone as a therapeutic target in patients with unstable asthma. It might also be an indication that this particular therapeutic target was not adequately treated (high S_{acin} values despite high doses of steroids), and the review data that we could obtain in a patient subgroup confirm this to some extent. These patients were discharged home on oral corticosteroids for between 3 and 5 days after discharge, with the net effect being that after review, only 2 of the 11 patients still had an S_{acin} value of greater than the upper limit of normal and that all patients had an S_{cond} value of less than the upper limit of normal (Table I). On the other hand, a very recent report on the considerable proportion of asthmatic patients who are persistently noneosinophilic²⁹ and for whom alternative controller treatments might be needed could explain residual high S_{acin} values in some patients with a high GINA score.

It has been suggested that the degree of air trapping is a significant prognostic factor in patients with severe asthma.^{27,30} When we compared the FVC (percent predicted) values between the patients with an exacerbation of asthma and those with stable asthma, for a given level of airflow obstruction (FEV₁/FVC ratio), FVC (percent predicted) values were less in the patients with an asthma exacerbation, suggesting greater gas trapping. These results are consistent with those of Sorkness et al,²⁷ who demonstrated in 287 patients with stable but severe asthma that the increase in FEV₁ (percent predicted) after bronchodilation was accompanied by an increased FVC (percent predicted) value

TABLE I. Demographics (mean [minimum-maximum 95% CI])

	Asthma exacerbation (n = 18, 5M/13F)	Stable asthma (n = 19, 13M/6F)	P value (stable vs asthma exacerbation)	Asthma exacerbation		P value (baseline vs review)
				Baseline (n = 11)	Review at 4 wk (n = 11)	
Age (y)	33 (25-55)	56 (48-61)	.004			
Height (cm)	163 (161-170)	175 (164-179)	.031			
Spirometry						
FEV ₁ (% predicted)	59 (45-75)	78 (70-85)	.001	75 (41-78)	89 (55-103)	.006
FVC (% predicted)	79 (73-94)	102 (94-112)	<.001	81 (72-100)	100 (93-112)	.003
FEV ₁ /FVC ratio (%)	60 (52-73)	62 (60-66)	>.1	66 (50-76)	70 (51-79)	>.1
MBW						
S _{acin} (% predicted)	225 (143-392)	209 (155-235)	>.1	238 (119-496)	107 (64-201)	.003
S _{cond} (% predicted)	185 (119-245)	92 (64-141)	.001	201 (129-312)	70 (53-114)	.01
FRC (% predicted)	93 (81-123)	91 (82-100)	>.1	96 (79-140)	97 (80-143)	>.1
No. of patients with S _{acin} >ULN	11/18	14/19	>.1	6/11	2/11	>.1
No. of patients with S _{cond} >ULN	10/18	2/19	.01	6/11	0/11	.02

Spirometry and small-airway function measurements (median [minimum-maximum 95% CI]) were performed in all 37 patients.

ULN, Upper limit of normal.

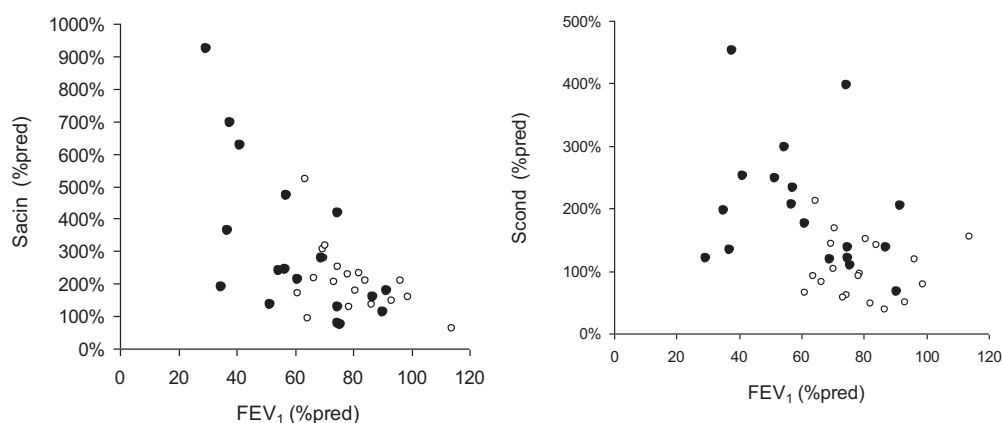


FIG 1. Left, S_{acin} (percent predicted) value as a function of FEV₁ (percent predicted) for the entire group. Right, S_{cond} (percent predicted) value as a function of FEV₁ (percent predicted). Solid circles represent the asthma exacerbation group, and open circles represent the stable asthma group.

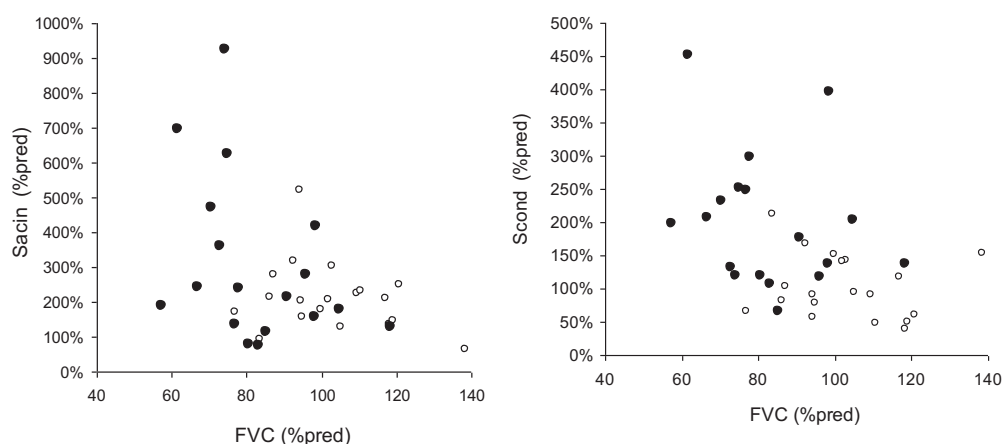


FIG 2. Left, S_{acin} (percent predicted) value as a function of FVC (percent predicted) for the entire group. Right, S_{cond} (percent predicted) value as a function of FVC (percent predicted). Solid circles represent the asthma exacerbation group, and open circles represent the stable asthma group.

over the entire range of FEV₁/FVC impairment, which was confirmed with measures of residual volume/total lung capacity ratio. The reason for the air trapping is likely due to small-airways

closure. However, in the multiple regression analysis neither S_{acin} nor S_{cond} values were retained as significant determinants of FVC (percent predicted) values within each asthma group (Table II).

TABLE II. Relative correlations between FEV₁ (or FVC) values and S_{acin} and S_{cond} values by using multiple regression

	Asthma exacerbation (n = 18)		Stable asthma (n = 19)		All asthma (n = 37)	
	R ² (adj) = 0.39	P value	R ² (adj) = 0.20	P value	R ² (adj) = 0.41	P value
S _{acin}						
FEV ₁	β = -0.84	.009	β = -0.72	.047	β = -0.91	<.001
FVC	Not retained		Not retained		Not retained	
S _{cond}						
FEV ₁	No variables retained		No variables retained		No variables retained	
FVC	No variables retained		No variables retained		No variables retained	

β, Partial correlation coefficient; R²(adj), Adjusted R² value of the multiple stepwise regression.

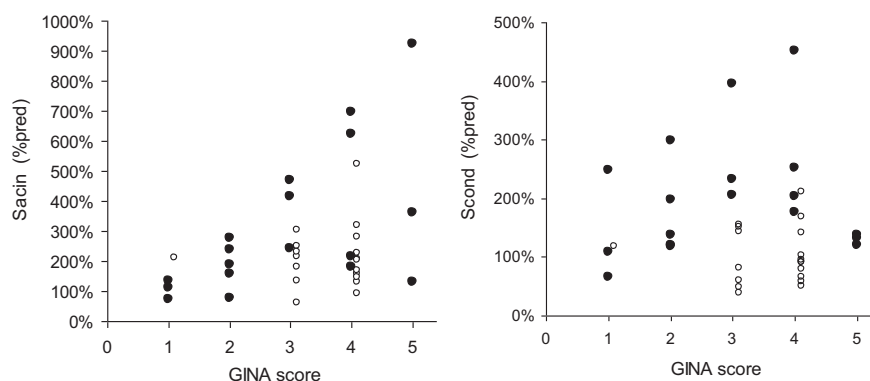


FIG 3. Left, S_{acin} (percent predicted) value as a function of GINA step score. Right, S_{cond} (percent predicted) value as a function of GINA step score. Solid circles represent the asthma exacerbation group, and open circles represent the stable asthma group.

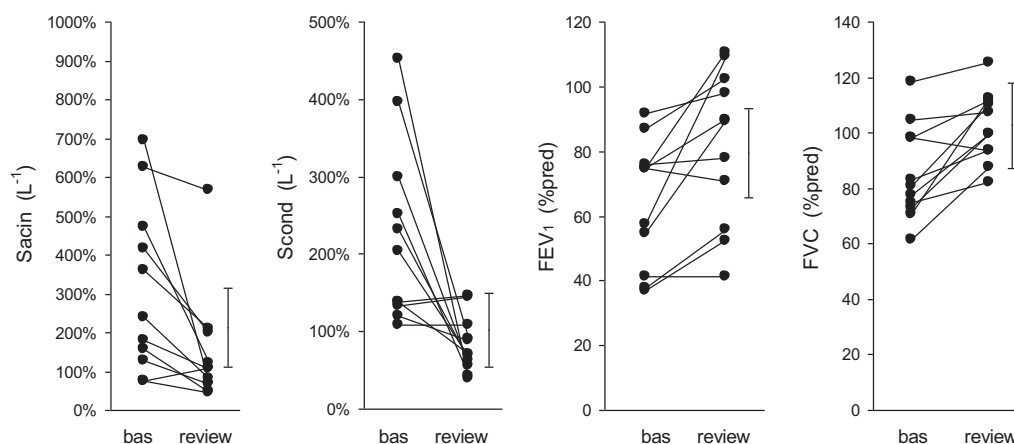


FIG 4. S_{acin}, S_{cond}, FEV₁ (percent predicted), and FVC (percent predicted) values during admission (bas) and after review in the subgroup of patients with a severe exacerbation of asthma who came back for the return visit (n = 11). Vertical bars represent the 95% CIs for these parameters obtained in the stable asthma group.

This suggests that the air trapping in the patients with unstable asthma occurs in a relatively homogeneous fashion across the lungs, and/or does not affect the degree of ventilation heterogeneity developing within the peripheral ventilated airspaces at or near FRC, or both. This is also supported by fact that FRC values did not change significantly in the unstable subgroup on review, despite a significant reduction in FVC values.

Several studies have demonstrated persistent abnormalities in the acinar compartment, despite adequate treatment. In a recent

structure-function study in patients with stable asthma receiving moderate-to-high doses of inhaled corticosteroids,¹⁷ a correlation was found between S_{acin} values and alveolar nitric oxide levels. Moreover, in a very recent study S_{acin} but not S_{cond} values predicted change in asthma control after a downtitration of inhaled corticosteroids.¹⁵ Berry et al³¹ have determined that alveolar nitric oxide levels are increased in patients with refractory asthma, suggesting that airway inflammatory processes potentially extend to the acinar airways/alveoli. By using state-of-the-art functional

magnetic resonance imaging techniques, the apparent diffusion coefficient is increased in asthmatic compared with nonasthmatic airways, indicating the presence of dysfunction of peripheral diffusion-dependent airways.³² Also, a loss of alveolar attachments has been demonstrated in patients with fatal asthma, with less elastic fibers in the adventitial walls of the small airways and peribronchial septa.³³ Similar loss of alveolar attachment in patients with nonfatal asthma, even if less severe, could further increase ventilation heterogeneity in the acinar zone. The S_{acin} values in our study could be the functional consequence of any of the above structural abnormalities in the partially or fully alveolated acinar airways. We postulate that the increased S_{acin} values observed in patients with asthma exacerbations are attributable to either permanent structural or corticosteroid-resistant inflammatory changes in the periphery of the lung, which will also lead to airflow obstruction.

Our results complement findings from an early physiologic study in children³⁴ in which patients with an abnormally steep nitrogen phase III slope obtained from a modified single-breath oxygen test (starting oxygen inhalation from FRC instead of residual volume) had the most severe clinical course over the year preceding the study. Although the authors interpreted these data on the basis of differences in time constants between different lung compartments that were far apart, recent modeling suggests that the phase III slope, as measured by Cooper et al,³⁴ is predominantly influenced by ventilation heterogeneity within smaller length scales (ie, within the acinus) and can therefore be considered a surrogate for S_{acin} values.²³ Hence this early study was in fact the first physiologic measurement indicating that the acinar lung zone could play an important part in asthma disease severity. A more recent study by Bourdin et al³⁵ in adult asthmatic patients used a vital capacity single-breath washout test and demonstrated a relationship between the number of exacerbations per year and the phase III slope. However, in the case of a vital capacity single-breath washout, it is impossible to assess the relative contributions from S_{acin} and S_{cond} values to the observed phase III slope.

The pathophysiologic implication of the present findings is that in patients with unstable asthma, the acinar component is associated with airflow obstruction in addition to a component of relatively increased S_{cond} values (Table I) but with the latter being independent of the level of airflow obstruction. Previous studies have consistently shown some degree of conductive airway abnormality in patients with asthma with a range of severities that responded poorly to inhaled β -agonist¹¹ and corticosteroid treatment.^{13,18} It is therefore tempting to speculate that the S_{cond} value is a functional reflection of the so-called remodeling process, which occurs early in the asthma disease process and might be long standing and poorly reversible with treatment.² Increased S_{cond} values in patients with an asthma exacerbation in particular might also be the functional result of eosinophilic inflammation of the airways, which could also explain why an intensified course of steroid treatment decreased S_{cond} values in the review subgroup.

During the past decade, the postulated implications of the small airways in the pathophysiology of asthma usually refer to the small conductive airways (approximately 2 mm in diameter), and experimental *in vivo* evidence is often based on high-resolution computed tomographic measurements.^{36,37} With the present study, we have demonstrated that at least part of the impaired functionality of the small airways is located more peripherally than the small conducting airways and that it is the airways within the acinus that demonstrate significant functional impairment that

are beyond the resolution of most imaging and spirometric techniques.

In conclusion, we have demonstrated that airway obstruction in asthmatic patients, as measured by impairment of FEV₁, is associated with impaired function of the airways within the acinus. In patients with acute severe asthma, S_{acin} values were also associated with treatment requirements and were shown to be partly reversible after a course of oral steroids. The finding that a major determinant of asthma severity is located in the acinar lung zone is novel and highlights the importance of targeting steroid or alternative therapies to this zone in asthmatic patients.

Key messages

- It has been suggested that the acinus is implicated, particularly in patients with severe asthma; however, actual measurements of airway functionality in this lung zone are currently lacking.
- This study shows that the S_{acin} value is a major contributor to airflow obstruction in patients with unstable asthma.
- Importantly, it is the acinar airways and not the small conducting airways that determine asthma severity based on treatment requirement.

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