

Effects of time, albuterol, and budesonide on the shape of the flow-volume loop in children with asthma

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Background: Assessment of asthma through spirometric analysis in children is challenging because of often normal FEV₁ values.

Objective: We used Mead's slope ratio (SR; $(d\dot{V}/dV)/(\dot{V}/V)$) to analyze the shape of the flow-volume loop.

Methods: We analyzed the effects of time, albuterol, and budesonide on FEV₁, FEV₁/forced vital capacity (FVC) ratio, forced expiratory flow from 25% to 75% of expired volume, and Mead's SR both early (between 75% and 50% of FVC, SR61) and late (between 75% and 50% of FVC, SR35) in exhalation in the Childhood Asthma Management Program cohort at baseline, 4 months, and the end of the study in participants who received either inhaled placebo or budesonide twice daily.

Results: In the placebo group both SR61 and SR35 improved over time. Bronchodilator consistently improved both SR61 and SR35, without change in degree of improvement over time. Similarly, in the budesonide group time and bronchodilator each independently improved both SR61 and SR35. At 4 months and the end of the study, patients receiving budesonide had significant improvements in SR61 relative to patients receiving placebo, which was independent of bronchodilator effect. Budesonide and placebo were not different with respect to prebronchodilator or postbronchodilator SR35.

Conclusion: Budesonide-treated patients have less concave flow-volume loops when compared with placebo-treated patients. Time and bronchodilator also make the flow-volume loop less concave. Furthermore, it appears that there are discrete bronchodilator- and corticosteroid-responsive components of airflow obstruction in pediatric asthma. (*J Allergy Clin Immunol* 2008;122:781-7.)

Key words: Spirometry, slope ratio, asthma, pediatric, children

Asthma is a chronic respiratory disease characterized by partially or completely reversible airflow obstruction, mucus hypersecretion, and increased airway hyperresponsiveness, all of which are believed to result from chronic airway inflammation.¹ The Childhood Asthma Management Program (CAMP) trial was designed specifically to evaluate the effects on lung growth, as determined by means of postbronchodilator FEV₁ of 3 inhaled treatments: budesonide (200 µg twice daily), nedocromil (8 mg twice daily), and placebo over a 4- to 6-year period in children 5 to 12 years of age with mild-to-moderate asthma.²

The CAMP results indicated that long-term budesonide treatment was not better than placebo in terms of effect on lung function, as measured by using FEV₁ percent predicted after bronchodilator administration.³ In contrast, budesonide treatment improved airway responsiveness to methacholine and resulted in significant reductions in asthma symptoms, β-agonist use, asthma hospitalizations, urgent care visits, and need for prednisone courses.³ The lack of improvement in FEV₁ percent predicted despite treatment with inhaled corticosteroid and clear clinical benefit in terms of hospitalizations, symptoms, and medication use led to further evaluation of the maximum expiratory flow-volume loop (MEFVL) data obtained in CAMP in an effort to reconcile these contrasting findings. We hypothesized that there was information about lung function in the MEFVL that was not captured by using standard measures (ie, FEV₁ percent predicted) and further hypothesized that this information might better reflect the improvements in disease burden seen in patients treated with inhaled corticosteroids.

The current study seeks to further define the pulmonary function abnormalities in the CAMP cohort at baseline and the effects of time in the study, treatment with albuterol, and treatment with budesonide on lung function. After a review of the literature regarding measures of lung function, especially those with relationships to alterations in expiratory flow, we chose to analyze the CAMP cohort's spirometric data by estimating Mead's slope ratio (SR) in early (between 75% and 50% of forced vital capacity [FVC], SR61) and late (between 75% and 50% of FVC, SR35) midexpiration.

Mead⁴ defined the SR as the slope of a tangent to the curve at a given point ($d\dot{V}/dV$), divided by the slope of the line drawn through that point and the curve at the residual volume (chord line, $\dot{V}/V$); thus $SR = (d\dot{V}/dV)/(\dot{V}/V)$ (Fig 1) and described it as a dimensionless ratio sensitive to the shape of the flow-volume curve. Here the SRs derived from the flow-volume loops are used to analyze the effects of time, bronchodilator, and inhaled corticosteroids on the shape of the MEFVL in patients from the CAMP study. Some of the results of these studies have been previously reported in the form of an abstract.⁵

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Abbreviations used

CAMP: Childhood Asthma Management Program
 COPD: Chronic obstructive pulmonary disease
 FEF₂₅₋₇₅: Forced expiratory flow from 25% to 75% of expired volume
 FVC: Forced vital capacity
 MEFVL: Maximal expiratory flow-volume loop
 SR: Slope ratio
 SR35: Slope ratio at 35% FVC
 SR61: Slope ratio at 61% FVC

METHODS**CAMP design**

Details of the design and methods of the CAMP study, including the characteristics of children at randomization, are published elsewhere.² One thousand forty-one children from 5 through 12 years of age with mild-to-moderate asthma were randomized to receive twice daily dosing of 200 µg of budesonide (n = 311), 8 mg of nedocromil (n = 312), or placebo (n = 418). All patients were treated with albuterol for symptoms and prednisone for exacerbations. Participants were treated for 4 to 6 years (mean ± SD, 4.3 ± 0.7 years). For the purposes of these analyses, only the placebo- and budesonide-treated groups were analyzed because budesonide had the most significant effects on lung function (spirometric measures at 4 months of treatment and methacholine responsiveness throughout the trial) and measures of asthma control.³

Spirometry

Spirometry was performed before the 28-day screening period and 3 times yearly during the study, with prebronchodilator and postbronchodilator measurements taken at each time point using equipment and testing protocols meeting or exceeding American Thoracic Society standards.^{6,7} Height, weight, sex, age, and race were recorded so that appropriate predicted normal values^{8,9} could be used to calculate spirometric indices as percentages of predicted values. Measurements were taken on study medication.

Interpolation of SRs

As detailed above, Mead⁴ defined the SR as $(d\dot{V}/dV)/(\dot{V}/V)$ (Fig 1). Permutt and Menkes¹⁰ later showed that SR at a given point on the flow-volume curve is equivalent to the slope of a log-log plot of flow against volume at that point. Thus the SR at a given point between 50% and 25% of FVC is approximately $\log(\dot{V}_{50}/FVC) - \log(\dot{V}_{25}/FVC) / \log 0.5 - \log 0.25$. We used this method to interpolate SRs between 25% and 50% of FVC and between 50% and 75% of FVC. Given their derivation from a log-log plot, we will use the midpoint between log 0.25 and log 0.5 (35%) and between log 0.75 and log 0.5 (61%) to place these approximations in expired volume (FVC). Thus the SR61 represents the curvature of the expiratory limb of the flow-volume loop between 75% and 50% inspired volume remaining, describing early to middle forced expiration. The SR35 represents the curvature of the expiratory limb of the flow-volume loop between 50% and 25% inspired volume remaining, describing middle to late forced expiration.

Statistical analysis

The statistical analyses are described in detail in the **Methods** section of this article's Online Repository available at www.jacionline.org. The degree of change in an outcome measure was determined by subtracting the baseline measurement from the measurement obtained at the last follow-up visit during the treatment period. The difference between the treatment group and the placebo group in each measure of change was determined by means of multiple linear regression,¹¹ with the change in the measure as the response variable, 2 indicator variables for the treatment groups, and adjustment for covariates. All analyses were performed with SAS software (version 6.12; SAS Institute, Inc,

Cary, NC). The *P* values presented are 2-sided and have not been adjusted for multiple comparisons.

RESULTS**Study population**

The budesonide- and placebo-treated groups were similar at baseline in terms of age, race, sex, asthma history, prior asthma therapy, prior morbidity, atopy, and airway hyperresponsiveness as measured by means of FEV₁ methacholine challenge (Table I).³ The duration of follow-up was similar as well, with a mean of 4.3 years for each group (Table I).

Baseline measures of spirometry and SR

At entry into the CAMP study, the mean prebronchodilator SR at 61% FVC (SR61) and SR at 35% FVC (SR35) were greater than 1, which is consistent with convex flow-volume loops. Although FEV₁ and FVC were within normal limits, the abnormal FEV₁/FVC ratio indicates airflow obstruction (Table I).

Effects of bronchodilator and time on SR in the placebo group

There were no significant changes in the prebronchodilator SR61 (Fig 2, A, and see Table E1 in this article's Online Repository available at www.jacionline.org) or SR35 (Fig 2, B, and Table E1) over the first 4 months in the study. However, by the end of the 4.3-year follow-up, significant improvement occurred in prebronchodilator SR61 (baseline vs 4.3 years, 1.32 vs 1.23; *P* < .0001) and SR35 (baseline vs 4.3 years, 1.27 vs 1.22; *P* = .0002) compared with baseline values (see Table E1).

Bronchodilator improved both SR61 and SR35 at all time points, as measured by mean change in SR with bronchodilator ([Postbronchodilator SR – Prebronchodilator SR] vs 0, *P* < .0001, Fig 2). The magnitudes of the improvements with bronchodilator in SR61 (Postbronchodilator SR61 – Prebronchodilator SR61) and SR35 (Postbronchodilator SR35 – Prebronchodilator SR35) did not change significantly over time (*P* = not significant for change over time, Fig 3, see Table E1). Similar to prebronchodilator values, there were no significant changes in postbronchodilator SR61 and SR35 over 4 months, and at the end of the study, there were significant improvements in postbronchodilator SR61 (baseline vs 4.3 years, 1.12 vs 1.04; *P* = .001; Fig 2, A; see Table E1) and SR35 (baseline vs 4.3 years, 1.15 vs 1.10; *P* = .002; Fig 2, B; see Table E1) compared with baseline values. Despite these significant beneficial effects of both time and bronchodilator on SR, postbronchodilator SR61 and SR35 in the placebo group remained greater than 1 at the end of the study, indicating the persistence of convexity in the MEFVL (Fig 2, see Table E1).

Effects of budesonide on SR

Over the duration of the study, both prebronchodilator and postbronchodilator SR61 improved in budesonide-treated patients significantly more than in patients treated with placebo (Figs 4, A and B; see Table E2 in this article's Online Repository available at www.jacionline.org). However, budesonide did not significantly affect the prebronchodilator or postbronchodilator SR35 at either time point (Figs 4, C and D; see Table E2).

Similar to the results in the placebo group, bronchodilator significantly improved both SR61 and SR35, as measured with the

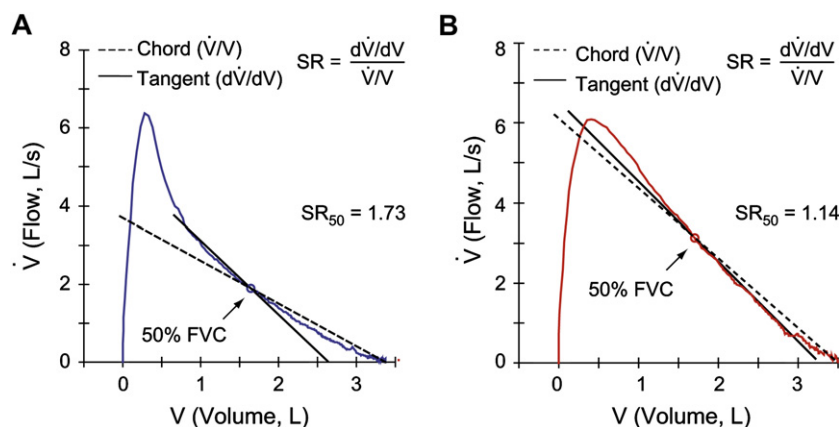


FIG 1. Prebronchodilator (**A**) and postbronchodilator (**B**) MEFVL curves with tangent ($d\dot{V}/dV$) and chord ($\dot{V}/V$) lines (broken and solid lines, respectively) fitted at 50% FVC. The ratio of their slopes, $(d\dot{V}/dV)/(\dot{V}/V)$, defines the SR at 50% FVC. Note that as the MEFVL curve becomes more linear after bronchodilator (Fig 1, B), the 2 slopes become more similar, and SR decreases towards 1, where the slopes are equal.

following equation: (Postbronchodilator SR – Prebronchodilator SR). The magnitude of the change in both SR61 and SR35 with bronchodilator in the budesonide-treated patients was not significantly different from that seen in the placebo-treated patients and did not change over time (Figs 3, A and B; see Table E3 in this article's Online Repository available at www.jacionline.org).

At the end of the study, the postbronchodilator SR61 in the budesonide group was significantly lower than that in the placebo group (postbronchodilator SR61: budesonide vs placebo, 0.98 vs 1.04; $P = .01$; Fig 4, B; see Table E2) and was less than and nearly equal to 1, indicating a near-linear MEFVL. Although prebronchodilator and postbronchodilator SR35 in the budesonide-treated patients did improve over time and with bronchodilator, at the end of the study, there were no significant differences in prebronchodilator or postbronchodilator SR35 when comparing the budesonide-treated patients with those receiving placebo (prebronchodilator SR35: budesonide vs placebo, 1.20 vs 1.22; $P = .44$; Fig 4, C; postbronchodilator SR35: budesonide vs placebo, 1.08 vs 1.10; $P = .17$; Fig 4, D; Table E2). Furthermore, analysis of baseline SRs finds no relationship between baseline SRs and effects of time, bronchodilator, or budesonide on SR (see Table E4 in this article's Online Repository available at www.jacionline.org).

Effects of time and bronchodilator on other spirometric measures in the placebo group

For comparison with analyses of SRs during the CAMP study, standard spirometric measures are included (see Table E5). In the placebo group over the 4.3 years of the study, neither prebronchodilator nor postbronchodilator values for either FEV₁ percent predicted or FVC percent predicted changed significantly. FEV₁/FVC ratio decreased both before and after bronchodilator in the placebo group (baseline vs 4.3 years, FEV₁/FVC: prebronchodilator, 79.9% vs 78.0%, $P < .0001$; postbronchodilator, 85.6% vs 83.9%, $P < .0001$). Forced expiratory flow from 25% to 75% of expired volume (FEF₂₅₋₇₅) percent predicted also decreased both before and after bronchodilator in the placebo group (baseline vs 4.3 years FEF₂₅₋₇₅ percent predicted: prebronchodilator, 67.9% vs 64.2%, $P = .0004$; postbronchodilator, 87.7% vs 80.4%, $P < .0001$).

In the placebo group FEV₁ percent reversibility ($[(\text{Postbronchodilator FEV}_1 - \text{Prebronchodilator FEV}_1)/\text{Prebronchodilator FEV}_1]$) did not change significantly at 4 months but decreased by the end of the study (10.6 vs 9.2, $P = .03$).

Effects of budesonide on standard spirometric measures

FEV₁ percent predicted, FVC percent predicted, FEF₂₅₋₇₅ percent predicted, and FEV₁/FVC ratio improved significantly in budesonide-treated patients in comparison with placebo treated patients both before and after bronchodilator at 4 months (see Table E6). The prebronchodilator improvements with budesonide treatment in these spirometric measures were still significant at the end of the study. After bronchodilator, FEV₁ percent predicted, FVC percent predicted, and FEV₁/FVC ratio were not significantly different between budesonide- and placebo-treated patients. Of the spirometric measures, only FEF₂₅₋₇₅ percentage showed a difference between the budesonide and placebo groups at the end of the study (budesonide vs placebo, 82.5 vs 80.0; $P = .04$; Table E6).

FEV₁ reversibility in the budesonide group was lower than in the placebo group at 4 months ($P < .001$) and at the end of the study ($P = .04$, see Table E6).

DISCUSSION

Assessment of airflow limitation in asthma

In 1949, Tiffeneau et al¹² first emphasized FEV₁ as an index of airflow limitation in chronic obstructive pulmonary disease (COPD). Subsequently, the development of the MEFVL in 1958 by Hyatt et al¹³ led to analysis of flow, volume, and time relationships in an effort to gather information about the sources and mechanisms of airflow limitation in both COPD and asthma. Results of this work include the use of FEV₁ and FEF₂₅₋₇₅¹⁴ as measures of airflow limitation.

In healthy adult subjects the expiratory flow-volume relationship, especially during midexpiration, is linear, which is consistent with a lung that empties as a single compartment. This linear emptying allows for the use of FEV₁ and FEF₂₅₋₇₅ as measures of airflow limitation, which is indicative of the entire course of

TABLE I. Baseline characteristics*

Characteristic†	Budesonide	Placebo
No. of patients	311	418
Age (y)	9.0 ± 2.1	9.0 ± 2.2
Race or ethnic group, no. (%)		
Non-Hispanic white	201 (64.6)	292 (69.9)
Non-Hispanic black	44 (14.1)	56 (13.4)
Hispanic	32 (10.3)	37 (8.9)
Other	34 (10.9)	33 (7.9)
Sex, no. (%)‡		
Female	130 (41.8)	184 (44.0)
Male	181 (58.2)	234 (56.0)
Age at onset of asthma (y)	3.1 ± 2.3	3.0 ± 2.6
Time since diagnosis of asthma (y)	5.2 ± 2.6	4.9 ± 2.7
Treatments in 6 mo before enrollment, no. of patients (%)		
Cromolyn or nedocromil	133 (42.8)	160 (38.3)
Inhaled corticosteroid	126 (40.5)	150 (35.9)
Oral corticosteroid	107 (34.4)	162 (38.8)
Severity of asthma, no. (%)		
Moderate	166 (53.4)	216 (51.7)
Mild	145 (46.6)	202 (48.3)
Hospitalizations for asthma in year before enrollment, no./100 person-years	31	31
Recordings on daily diary card		
Episode-free days, no./mo§	9.7 ± 7.8	9.6 ± 7.6
Use of albuterol for symptoms, puffs/wk	10.4 ± 9.8	10.2 ± 9.6
Night awakenings, no./mo	0.9 ± 1.7	0.8 ± 1.5
FEV ₁ before bronchodilator use (% predicted)	93.6 ± 14.4	94.2 ± 14.0
FEV ₁ after bronchodilator use (% predicted)	103.2 ± 13.2	103.3 ± 12.2
FEV ₁ /FVC before bronchodilator use (%)	79.4 ± 8.7	80.1 ± 8.7
FEV ₁ /FVC after bronchodilator use (%)	85.2 ± 6.6	85.8 ± 7.1
Airway responsiveness to methacholine (FEV ₁ PC ₂₀), mg/mL	1.1 ± 3.3	1.1 ± 3.3
Height (%)	56.8 ± 28.0	55.3 ± 28.8
SR61 before bronchodilator use	1.33 ± 0.41	1.31 ± 0.41
SR61 after bronchodilator use	1.11 ± 0.38	1.11 ± 0.47
SR35 before bronchodilator use	1.30 ± 0.29	1.27 ± 0.32
SR35 after bronchodilator use	1.19 ± 0.30	1.15 ± 0.34

*Values are presented as means ± SD where shown. Not all percentages add to 100 because of rounding or because some children used more than 1 treatment before enrollment.

†FEV₁PC₂₀ denotes the concentration of methacholine that caused a 20% decrease in FEV₁.

‡P value for homogeneity among groups = .02.

§An episode-free day was defined as a day with no nighttime awakenings, morning and evening peak flow of greater than 80% of personal best peak flow (determined by algorithm 12), no use of albuterol for symptoms, no use of prednisone, no absence from school or contact with a physician because of asthma symptoms, and no episode of wheezing, coughing, chest tightness, or shortness of breath.

||Values are geometric means ± SD.

expiration. However, as Pride et al¹⁵ and Mead⁴ continued their evaluation of the expiratory flow-volume relationship and considerations of lung physiology in general, the limitations of a single-compartment model of the lung in modeling disease became apparent.

In a healthy lung the rate constants of emptying will be identical throughout the forced expiration and would be expressed as a

linear expiratory flow-volume loop, as seen in healthy adults. However, in diseased lungs it is well recognized that emptying is nonuniform throughout volume, resulting in a curvilinear flow-volume relationship, as seen in COPD,^{16,17} cystic fibrosis,¹⁸ primary pulmonary hypertension,¹⁹ and asthma.^{18,20,21} This non-linearity is believed to reflect either the existence of multiple compartments in the lung with different rate constants of emptying or a dynamic obstruction applied uniformly across the lung units, also referred to as parallel dynamic airway compression. Although FEV₁ accurately measures airflow and can detect airflow limitation, these changes in MEFVL shape precede abnormalities in FEV₁ in the course of airway disease.²²

The relative insensitivity of FEV₁ to changes in expiratory flow over the entire course of lung emptying led to further analysis of forced expiratory flow within the time domain through time constants²³ and analysis of the geometric configuration of the expiratory flow-volume loop through Mead's SR.²² Both time constants and Mead's SRs were found to be more sensitive than FEV₁ or mid-maximal expiratory flow to early airway changes, as seen in asymptomatic smokers compared with asymptomatic nonsmokers.¹⁰

Present findings

Natural history of SR in childhood asthma. In the analyses of the placebo-treated group over time, we found that there is an improvement over time in the convexity of the flow-volume loop, as measured by using both SR61 and SR35. This improvement is not seen at 4 months but is significant at the end of the study both before and after bronchodilator (see Table E1). Thus despite these patients not having received continuous budesonide therapy, they still had an improvement in their airflow limitation, independent of bronchodilator treatment. The improvement in SRs over time might be caused by an increase in airway caliber caused by growth, which confers protection from factors that produced airflow obstruction in smaller airways. A second explanation is that continued alveolarization of lung units leads to a lung with an overall slower but more homogeneous emptying. Notable in this change over time is the lack of significant improvement in any of the traditional metrics of lung function. Lack of improvement in FEV₁ relative to that seen in healthy children while SRs improve suggests that FEV₁ percent predicted is not sensitive to changes in the rate of lung emptying.

Effects of bronchodilator on SR. Albuterol is a short-acting β-agonist that has been used to treat asthma since the late 1960s,²⁴⁻²⁶ primarily through its well-established effects on bronchial smooth muscle. By relaxing bronchial smooth muscle, airway diameter increases, and airflow limitation is improved. Although albuterol has been noted to improve lung function, as measured by means of spirometry, in children with asthma since 1969,²² no studies have been done on the effects of albuterol on SR. O'Donnell et al²¹ studied the effects of isoproterenol on SR in asthma and noted that the configuration of the MEFVL does change toward linearity with isoproterenol use. Similarly, in the CAMP cohort there was a consistent improvement of approximately −0.2 in SR61 and −0.1 in SR35 with albuterol administration, regardless of time or treatment group ($P < .0001$).

Effects of budesonide on SR. In the original analysis of the CAMP data,³ the authors make the unexpected finding that

Placebo Group: —▲— Post-Bronchodilator —△— Pre-Bronchodilator

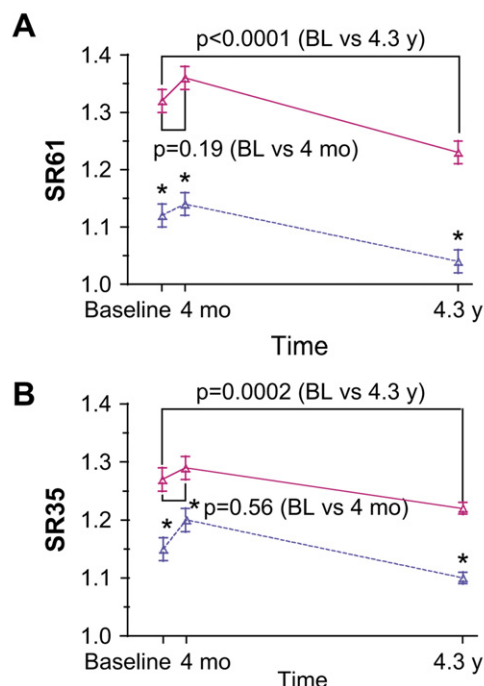


FIG 2. Effects of time and bronchodilator on SR in the placebo group. The placebo group's SR61 (**A**) and SR35 (**B**) before (magenta) and after (blue) bronchodilator are plotted. *P* values on the graph reflect comparisons of prebronchodilator SR61 and SR35 between time points as marked. *The mean changes before to after bronchodilator for SR61 and SR35 are greater than 0 at all time points ($P < .0001$). BL, Baseline.

budesonide did not improve lung function, as measured by means of FEV₁ percent predicted after bronchodilator at the end of the 4.3-year treatment interval when compared with that seen in placebo-treated patients. In contrast to this finding, postbronchodilator SR61 is significantly improved in the budesonide group compared with the placebo group (see Table E2), reflecting linearization of the flow-volume relationship early in exhalation, which is consistent with a reduction of airflow limitation.

In contrast, we did not find a significant difference in SR35 at the end of the study between budesonide- and placebo-treated patients before or after bronchodilator (before bronchodilator: 1.20 vs 1.22, $P = .44$; after bronchodilator: 1.08 vs 1.10, $P = .17$). This might reflect poor delivery of drug to late-emptying airways, the presence of a non-steroid-responsive pathology in these airways, or other mechanisms not yet elucidated. Further study of the CAMP cohort, including evaluation of the differences between patients who did have improvement in SR35 and those who did not might help elucidate mechanisms of airflow limitation in late expiration and provide further guidance for the development of new strategies to improve end-expiratory flow delay.

Differing effects of time, bronchodilator, and budesonide

As reported above, both time and bronchodilator treatment improve SR61 and SR35 in the placebo group. Given that SR61 and SR35 both before and after bronchodilator improve

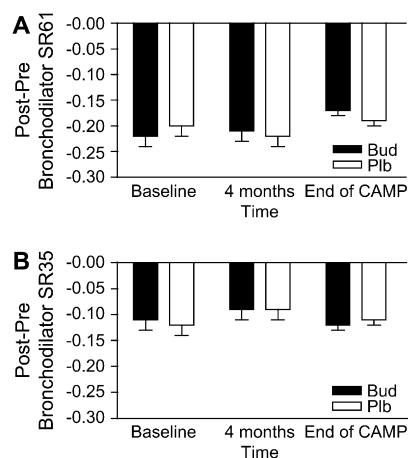


FIG 3. Effects of bronchodilator on SR. Changes in SR61 (**A**) and SR35 (**B**) with bronchodilator ([Postbronchodilator SR] – [Prebronchodilator SR]) for budesonide (*Bud*)– and placebo (*Plb*)–treated patients. Comparisons between the placebo- and budesonide-treated groups at marked time points were all statistically insignificant for both postbronchodilator/prebronchodilator SR61 and SR35. The mean postbronchodilator/prebronchodilator SR61 and SR35 are greater than 0 at all time points ($P < .0001$).

significantly in placebo-treated patients over the course of the study (see Table E1) and that the effects of bronchodilator on SR61 and SR35 do not change significantly over the 4.3 years of the study (see Table E3), these data suggest that the effects of time and bronchodilator are both independent and additive. Given that there is a significant difference in postbronchodilator SR61 in placebo- and budesonide-treated patients (see Table E2) and the lack of significant difference in postbronchodilator-prebronchodilator SR61 between placebo- and budesonide-treated patients (see Table E3), the effects of budesonide and bronchodilator are both independent and additive. Although our findings do not conclusively prove that time (reflecting lung growth, development, and remodeling), response to bronchodilator (reflecting relaxation of airway smooth muscle), and inhaled corticosteroids (reflecting reduction in airway inflammation) work through different mechanisms, it is plausible that they do.

Although inhaled corticosteroid treatment did not significantly change SR35, bronchodilator does consistently. Because SR35 reflects the time rate of lung emptying and thus airflow limitation late in expiration and because asthma is classically described as a disease of the “peripheral airways”^{27,28} generally thought to empty late, one of the more intriguing findings of this study is the finding that although budesonide treatment does not appear to improve MEFVL convexity late in expiration, albuterol does. This might reflect either different mechanisms of action or might indicate the lack of deposition of the inhaled corticosteroids in the lung periphery.

Comparison between SR and FEF₂₅₋₇₅

SR measures MEFL shape in terms of deviation from perfect single exponential emptying of the lung. FEF₂₅₋₇₅ has long been described as a measure that reflects the behavior of distal or “small” airways airflow obstruction.¹⁴ In the CAMP cohort budesonide treatment improved FEF₂₅₋₇₅ percent predicted and SR61 but not SR35. This indicates that the observed improvements in FEF₂₅₋₇₅ percent predicted can be related only to changes in early,

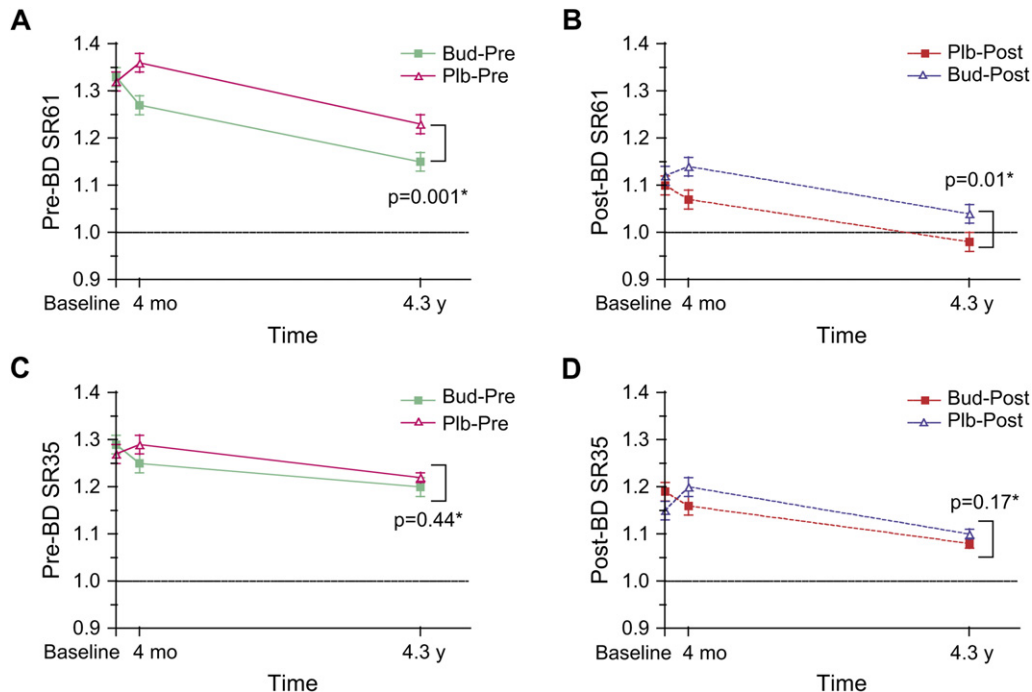


FIG 4. Effects of time, bronchodilator, and budesonide on SR. Prebronchodilator values (solid lines) for SR61 (A) and SR35 (C) and postbronchodilator values (dashed lines) for SR61 (B) and SR35 (D) are plotted for both budesonide-treated (squares) and placebo-treated (triangles) patients. *P values reflect significance of comparison at the end of the study between budesonide- and placebo-treated patients adjusted for changes from baseline.

but not late, emptying, reflecting an important limitation of FEV₂₅₋₇₅ in assessing the site of effect of therapy.

Limitations of the present findings

A limitation of this study is the unavailability of longitudinally measured normal values for SR61 and SR35. Without these data, we cannot compare the expected values or changes over time in SR in healthy children with those in our asthmatic cohort. However, given the improvements seen with bronchodilator and budesonide, both consistent with their known mechanisms of action in asthma, these results provide a starting point for the evaluation of the shape of the MEFVL by SR in patients with asthma and other lung diseases and healthy individuals. Another limitation is the use of Permutt's interpolation of SR, which might not be precisely the same as using a single point along the flow-volume tracing. Therefore we were limited to measuring SRs in the log-transformed midpoints of the second and third quarters of expiration.

Conclusion

These data suggest several interesting findings. First is the finding that over time, the natural history of the shape of the MEFVL in children with asthma is one of improvement. That postbronchodilator FEV₁ percent predicted did not improve in the CAMP cohort suggests that improvement in MEFVL convexity does not necessarily translate into improved peak expiratory flow. Further longitudinal study and comparison with healthy individuals will be necessary to determine the natural history and significance of changes in SR over time.

Second is the finding that inhaled corticosteroids appear to improve lung function through different mechanisms than bronchodilators and that those effects can be measured independently of one another by use of the SR.

Third is that SR is a more sensitive index for assessment of flow dynamics and its response to treatment in asthmatic children than the current gold standard, FEV₁ percent predicted.

Similarly, although FEF₂₅₋₇₅ has been long held as a measure of "small-airways" obstruction, the improvements in FEF₂₅₋₇₅ seen with budesonide and bronchodilator in the CAMP cohort are due to improvements in early flow, as measured by SR61, rather than late flow, as measured by SR35. This finding is important because although by definition FEF₂₅₋₇₅ measures the average flow over midexpiration (from 25% through 75% of expired volume), it has been described as reflecting distal airways and late-flow events. Our data show that FEF₂₅₋₇₅ can reflect changes primarily in early flow rather than late flow.

To fully determine the significance of these findings, there needs to be study of healthy children and adults to define the natural history of the normal time distribution of expiratory flow. Also, SR analysis combined with FEV₁ percent predicted might allow for improved prediction of asthma outcomes, allowing for refined treatment guidelines. Other diseases of airway obstruction (ie, cystic fibrosis and COPD) would also be amenable to SR analysis of MEFVL.

Questions of these sorts would be best answered by studies in which the spirometric equipment used captures moment-to-moment flow, time, and volume data digitally, so that accurate SRs of Mead⁴ can be calculated directly rather than being estimated. Furthermore, such measurement would also allow for other, potentially more accurate measurements of the time

distribution of expiratory flow, such as moments analysis, to be carried out. Although FEV₁ reliably reflects airflow limitation and is well known to predict asthma outcomes, our findings show that measurements of MEFVL shape can provide other information about the state of the lung in asthma. Furthering the work of Mead,⁴ Permutt and Menkes,¹⁰ and others in understanding the distribution of expiratory flow over volume and time in airway diseases might provide a better understanding of these diseases.

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Clinical implications: Changes in flow-volume loop shape in children with asthma can reflect changes in airflow for which SR might be more sensitive than conventional measures.

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METHODS

Statistical analyses

Data from the 2 inhaler-matched placebo groups (one for budesonide, $n = 208$; one for nedocromil, $n = 210$) were pooled after we determined that the children in the 2 groups were similar with respect to baseline characteristics and outcomes. Each participant was included in his or her assigned study group, regardless of any adjustments of treatment that occurred by protocol during the trial (intention-to-treat analysis).

The degree of change in an outcome measure was determined by subtracting the baseline measurement from the measurement obtained at the last follow-up visit during the treatment period. The difference between the treatment and the placebo groups in each measure of change was determined by means of multiple linear regression,^{E1} with the change in the measure as the response variable, 2 indicator variables for the treatment groups, and the following 8 covariates: the baseline value of the outcome measure, the child's age at randomization, race (2 indicator variables), sex, clinic (7 indicator variables), duration of asthma at baseline, severity of asthma at baseline, and skin test reactivity at baseline (any reactivity vs none). The adjusted mean change in each outcome measure in each study group was computed from the regression model by the use of mean values for all covariates.^{E2} All analyses were performed with SAS software (version 6.12). The P values presented are 2-sided and have not been adjusted for multiple comparisons.

In the comparisons among the study groups, we used regression models to adjust for small imbalances in baseline measures; however, unadjusted analyses for all outcome measures yielded qualitatively similar results.^{E3}

In Figs 1-3, plotted values are group means adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin test reactivity, and error bars indicate SEM.

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TABLE E1. Effects of time and bronchodilator on SR in the placebo group

	Baseline	SE	4 mo	SE	End of CAMP	SE	P value, baseline vs 4 mo	P value, baseline vs 4.3 y
Prebronchodilator SR61	1.32	0.02	1.36	0.02	1.23	0.02	.19	<.0001
Postbronchodilator SR61	1.12	0.02	1.14	0.02	1.04	0.02	.52	.001
Postbronchodilator-prebronchodilator SR61*	−0.20	0.02	−0.22	0.02	−0.19	0.01	.58	.38
Prebronchodilator SR35	1.27	0.02	1.29	0.02	1.22	0.01	.56	.0002
Postbronchodilator SR35	1.15	0.02	1.20	0.02	1.10	0.01	.13	.002
Postbronchodilator-prebronchodilator SR35*	−0.12	0.02	−0.09	0.02	−0.11	0.01	.27	.77

Values indicate the mean and SE of the mean SRs in the placebo group at study entry (*Baseline*), 4 months into the study, and 4.3 years (*end of CAMP*). Means are adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin test reactivity. For comparisons between time points, *P* values are based on changes from baseline.

**P* values for significance of difference between prebronchodilator and postbronchodilator SR61 and SR35 were less than .0001.

TABLE E2. Effects of budesonide on SR

Variable	Budesonide		Placebo		P value, BUD vs PLB*
	Adjusted mean*	SE	Adjusted mean*	SE	
SR61†					
Prebronchodilator					
Baseline	1.33	0.02	1.32	0.02	.76
Four months' follow-up	1.27	0.02	1.36	0.02	.001
End of CAMP	1.15	0.02	1.23	0.02	.001
Postbronchodilator					
Baseline	1.10	0.02	1.12	0.02	.70
Four months' follow-up	1.07	0.02	1.14	0.02	.007
End of CAMP	0.98	0.02	1.04	0.02	.01
Postbronchodilator-prebronchodilator					
Baseline	−0.22	0.02	−0.20	0.02	.46
Four months' follow-up	−0.21	0.02	−0.22	0.02	.75
End of CAMP	−0.17	0.01	−0.19	0.01	.44
SR35‡					
Prebronchodilator					
Baseline	1.29	0.02	1.27	0.02	.27
Four months' follow-up	1.25	0.02	1.29	0.02	.09
End of CAMP	1.20	0.02	1.22	0.01	.44
Postbronchodilator					
Baseline	1.19	0.02	1.15	0.02	.15
Four months' follow-up	1.16	0.02	1.20	0.02	.08
End of CAMP	1.08	0.01	1.10	0.01	.17
Postbronchodilator-prebronchodilator					
Baseline	−0.11	0.02	−0.12	0.02	.63
Four months' follow-up	−0.09	0.02	−0.09	0.02	.92
End of CAMP	−0.12	0.01	−0.11	0.01	.59

Values represent group means. Means are adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin test reactivity.

*For outcomes during follow-up, P values are based on changes from baseline.

†SR at FVC61% = $[\log(\text{FEF@FVC75\%/FVC}) - \log(\text{FEF@FVC50\%/FVC})]/[\log 0.75 - \log 0.50]$.

‡SR at FVC35% = $[\log(\text{FEF@FVC50\%/FVC}) - \log(\text{FEF@FVC25\%/FVC})]/[\log 0.50 - \log 0.25]$.

TABLE E3. Effects of bronchodilator on SR

	Bud post-pre BD SR61*	SE	Plb post-pre BD SR61*		SE	P value, BUD vs PLB
Baseline	−0.22	0.02	−0.20		0.02	.46
4 mo	−0.21	0.02	−0.22	†	0.02	.75
End of CAMP	−0.17	0.01	−0.19	‡	0.01	.44

	Bud post-pre BD SR35*	SE	Plb post-pre BD SR35*		SE	P value, BUD vs PLB
Baseline	−0.11	0.02	−0.12		0.02	.63
4 mo	−0.09	0.02	−0.09	†	0.02	.92
End of CAMP	−0.12	0.01	−0.11	‡	0.01	.59

Values represent group means. Means are adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin test reactivity.

*At all time points, in both the budesonide- and placebo-treated groups, the mean change in SR (Postbronchodilator − Prebronchodilator) is significantly different from zero ($P < .0001$).

†Comparison of baseline versus 4 months: placebo postbronchodilator-prebronchodilator SR61, $P = .58$. Baseline versus 4 months: placebo postbronchodilator-prebronchodilator SR35, $P = .27$.

‡Comparison baseline versus 4.3 years: placebo postbronchodilator-prebronchodilator SR61, $P = .38$. Baseline versus 4.3 years: placebo postbronchodilator-prebronchodilator SR35, $P = .77$.

TABLE E4. Effects of budesonide on SR subgrouped by quartiles of SR at baseline

Variable	Adjusted means by SR at baseline								P value*
	Quartile 1		Quartile 2		Quartile 3		Quartile 4		
	Bud	Plb	Bud	Plb	Bud	Plb	Bud	Plb	
SR61†									
Prebronchodilator									
Four months' follow-up	1.00	1.05	1.18	1.30	1.36	1.49	1.56	1.59	.60
End of CAMP	0.90	1.00	1.15	1.19	1.22	1.31	1.34	1.45	.95
Postbronchodilator									
Four months' follow-up	0.73	0.80	0.93	1.01	1.12	1.27	1.48	1.52	.31
End of CAMP	0.74	0.76	0.87	0.96	1.07	1.14	1.29	1.33	.07
Postbronchodilator-prebronchodilator									
Four months' follow-up	−0.28	−0.30	−0.25	−0.24	−0.16	−0.18	−0.18	−0.13	.40
End of CAMP	−0.22	−0.24	−0.24	−0.23	−0.09	−0.15	−0.15	−0.12	.07
SR35‡									
Prebronchodilator									
Four months' follow-up	1.04	1.11	1.20	1.24	1.31	1.33	1.41	1.55	.95
End of CAMP	1.05	1.05	1.14	1.20	1.20	1.27	1.35	1.37	.73
Postbronchodilator									
Four months' follow-up	0.93	0.99	1.16	1.14	1.19	1.30	1.41	1.37	.14
End of CAMP	0.91	0.98	1.07	1.07	1.10	1.15	1.26	1.21	.003
Postbronchodilator-prebronchodilator									
Four months' follow-up	−0.10	−0.14	−0.11	−0.11	−0.18	−0.10	0.02	−0.02	.81
End of CAMP	−0.17	−0.14	−0.12	−0.11	−0.07	−0.12	−0.10	−0.07	.22

Means are adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin test reactivity.

Bud, Budesonide; Plb, placebo.

*Derived from test of interaction of indicator variable for budesonide versus placebo × quartile of SR at baseline treated as an ordinal variable in which outcomes are changes from baseline.

†SR at FVC61% = $[\log(\text{FEF@FVC75\%/FVC}) - \log(\text{FEF@FVC50\%/FVC})]/[\log 0.75 - \log 0.50]$.

‡SR at FVC35% = $[\log(\text{FEF@FVC50\%/FVC}) - \log(\text{FEF@FVC25\%/FVC})]/[\log 0.50 - \log 0.25]$.

TABLE E5. Effects of time and bronchodilator on spirometry in the placebo group

	Baseline	SE	4 mo	SE	End of CAMP	SE	<i>P</i> value, baseline vs 4 mo	<i>P</i> value, baseline vs 4.3 y
Prebronchodilator FEV ₁ (% predicted)	93.9	0.7	93.2	0.5	94.8	0.6	0.57	0.14
Postbronchodilator FEV ₁ (% predicted)	103.2	0.6	102.6	0.4	103.0	0.5	0.73	0.90
FEV ₁ reversibility [(postbronchodilator FEV ₁ – prebronchodilator FEV ₁)/prebronchodilator FEV ₁] (%)	10.6	0.5	11.3	0.5	9.3	0.4	0.35	0.03
Prebronchodilator FVC (% predicted)	103.8	0.6	104.2	0.4	107.5	0.5	0.41	<0.0001
Postbronchodilator FVC (% predicted)	106.4	0.4	106.6	0.4	107.5	0.5	0.56	0.06
Prebronchodilator FEV ₁ /FVC (%)	79.9	0.4	78.7	0.3	78.0	0.3	0.003	<0.0001
Postbronchodilator FEV ₁ /FVC (%)	85.6	0.3	85.0	0.2	83.9	0.3	0.10	<0.0001
Prebronchodilator FEF ₂₅₋₇₅ (% predicted)	67.9	1.1	65.9	1.1	64.2	1.0	0.05	0.0004
Postbronchodilator FEF ₂₅₋₇₅ (% predicted)	87.7	1.1	85.8	1.2	80.4	1.0	0.08	<0.0001

Values indicate mean and SE of the mean for the placebo group of each spirometric index at study entry (baseline), 4 months into the study, and 4.3 years (end of study). Means are adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin-test reactivity. For comparisons between time points, *P* values are based on changes from baseline.

TABLE E6. Effects of budesonide, time, and bronchodilator on spirometry

Variable	Budesonide		Placebo		P value, budesonide vs placebo*
	Adjusted mean*	SE	Adjusted mean*	SE	
N					
Baseline	304	—	411	—	—
4 mo follow-up	293	—	396	—	—
End of CAMP	302	—	408	—	—
FVC (% predicted)					
Prebronchodilator					
Baseline	104.4	0.7	103.8	0.6	0.53
4 mo follow-up	106.3	0.5	104.2	0.4	0.002
End of CAMP	106.3	0.6	106.4	0.5	0.86
Postbronchodilator					
Baseline	107.1	0.7	106.4	0.6	0.43
4 mo follow-up	107.9	0.4	106.6	0.4	0.02
End of CAMP	107.2	0.5	107.5	0.5	0.72
FEV₁ (% predicted)					
Prebronchodilator					
Baseline	93.9	0.8	93.9	0.7	0.96
4 mo follow-up	98.4	0.6	93.2	0.5	<0.0001
End of CAMP	96.6	0.6	94.8	0.6	0.03
Postbronchodilator					
Baseline	103.4	0.7	103.2	0.6	0.81
4 mo follow-up	105.8	0.5	102.6	0.4	<0.0001
End of CAMP	103.7	0.6	103.0	0.5	0.33
FEV₁/FVC (%)					
Prebronchodilator					
Baseline	79.6	0.5	79.9	0.4	0.61
4 mo follow-up	81.4	0.3	78.7	0.3	<0.0001
End of CAMP	79.5	0.4	78.0	0.3	0.004
Postbronchodilator					
Baseline	85.3	0.4	85.6	0.3	0.52
4 mo follow-up	86.5	0.2	85.0	0.2	<0.0001
End of CAMP	84.5	0.3	83.9	0.3	0.14
FEF₂₅₋₇₅ (% predicted)					
Prebronchodilator					
Baseline	66.8	1.3	67.8	1.1	0.54
4 mo follow-up	73.0	0.9	65.3	0.8	<0.0001
End of CAMP	67.4	0.9	63.7	0.8	0.003
Postbronchodilator					
Baseline	87.4	1.3	87.7	1.1	0.88
4 mo follow-up	92.3	0.9	85.5	0.8	<0.0001
End of CAMP	82.5	0.9	80.0	0.8	0.04
FEV₁ reversibility [(postbronchodilator FEV₁ – prebronchodilator FEV₁)/prebronchodilator FEV₁]*%					
Baseline	11.2	0.6	10.6	0.5	0.51
4 mo follow-up	8.5	0.5	11.1	0.5	<0.0001
End of CAMP	8.0	0.5	9.2	0.4	0.04

Values represent group means. Means are adjusted for baseline values of age, race, sex, clinic, duration of asthma, severity of asthma, and skin-test reactivity.

*For outcomes during follow-up, P values are based on changes from baseline.