

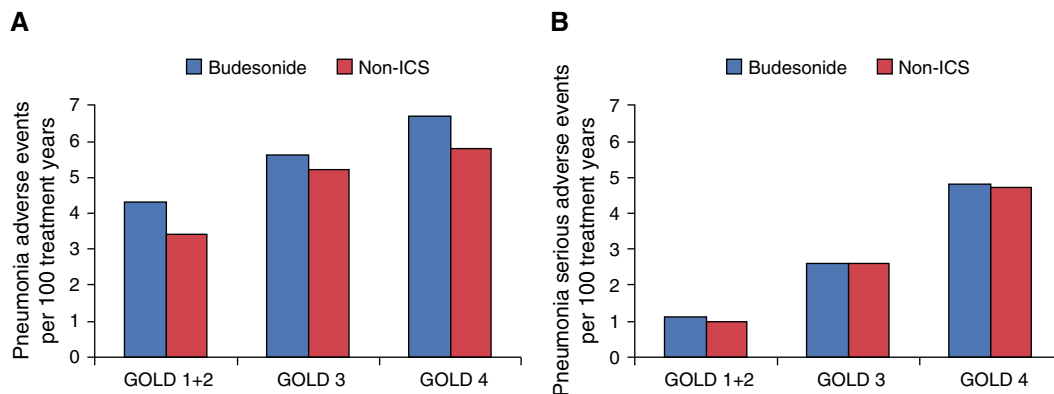


Figure 1. Pneumonia reported as adverse events (A) or serious adverse events (B) for subjects treated with budesonide (blue) or placebo (red) separated by Global Initiative for Chronic Obstructive Lung Disease (GOLD) Spirometry Severity. No differences for budesonide versus non-inhaled corticosteroids reached statistical significance. See Table 1 for confidence intervals.

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The Effects of Repeated Bronchoprovocation on FEV₁ in Subjects with Asthma

To the Editor:

A previous study (1) has reported that even a single airway challenge with inhaled methacholine or allergen results in increases in indices of airway wall remodeling in subjects with asthma. These indices include collagen type III deposition in the airway wall and increased numbers of airway goblet cells, both of which can increase resistance to airflow. This finding is concerning, given that both interventions are frequently employed to assess airway reactivity in research studies and even in the clinical setting.

We measured baseline FEV₁ collected between 2002 and 2013 from all eligible subjects recruited for asthma studies requiring methacholine testing. All studies were approved by the Hamilton Integrated Research Ethics Board (Hamilton, ON, Canada). Subjects were nonsmoking men and women, 18 to 60 years of age, with mild, stable asthma (FEV₁ ≤ 70% predicted, methacholine provocative concentration of methacholine causing a 20% fall in FEV₁ ≤ 16 mg/ml) and using only inhaled short-acting β₂-agonists. Subject demographics are given in Table 1. Each subject underwent

baseline methacholine testing by inhaling doubling concentrations during 2 minutes of tidal breathing (2). The results of these studies have been previously reported in the form of an abstract (3).

The data were grouped according to those subjects who received at least 2 methacholine tests (n = 111), at least 5 tests (n = 54), and at least 10 tests (n = 21). Each group was analyzed by repeated-measures analysis of variance, and the group mean (95% confidence interval [CI]) FEV₁ values were plotted. The initial mean FEV₁ was 94.3% predicted (range, 67.4–127.0).

The first two baseline methacholine tests were separated by a mean of 103 days (95% CI: 78, 128 d); the mean FEV₁ values were 3.52 L (95% CI: 3.39, 3.66 L) and 3.49 L (95% CI: 3.36, 3.62 L) (P = 0.04), respectively (Figure 1A).

The first and fifth baseline methacholine tests were separated by a mean of 686 days (95% CI: 492–880 d); the first and tenth tests were separated by a mean of 1,238 days (95% CI: 1,009–1,467 d). There was no evidence of a decrease in FEV₁ (P > 0.05) with repeated methacholine challenges (Figures 1B and 1C).

Twelve of the 111 subjects (7 female; 5 male) participated in repeated studies for periods in excess of 3.5 years. Their FEV₁ values (% predicted) are all shown in Figure 2. Linear regression for these individuals (colored lines in Figure 2) assessed change over the course of their participation in our studies. The average slope of the plot of FEV₁ versus time is 0.49 (SD, 0.92), which is not significantly different from zero (P > 0.05).

Collectively, these data show that repeated bronchoconstrictor provocation with methacholine does not change lung function. This is not consistent with any persistent clinically relevant airway wall remodeling.

The subjects in the current study all had mild stable asthma, usually of several years' duration. The data displayed here represent only the baseline measurements. Each baseline measurement was then accompanied by several other provocations with methacholine and/or

Table 1. Demographic details of subjects in study

	Age (yr)	Height (cm)	Methacholine PC ₂₀	FEV ₁ /FVC ratio	FEV ₁ % predicted
Mean	24.45	170.10	2.43	80.76	94.07
SD	7.77	9.09	0.08–27.9	8.57	11.94

Definition of abbreviation: methacholine PC₂₀ = provocative concentration of methacholine causing a 20% fall in FEV₁.

Note: n = 111 study subjects (69 female, 42 male).

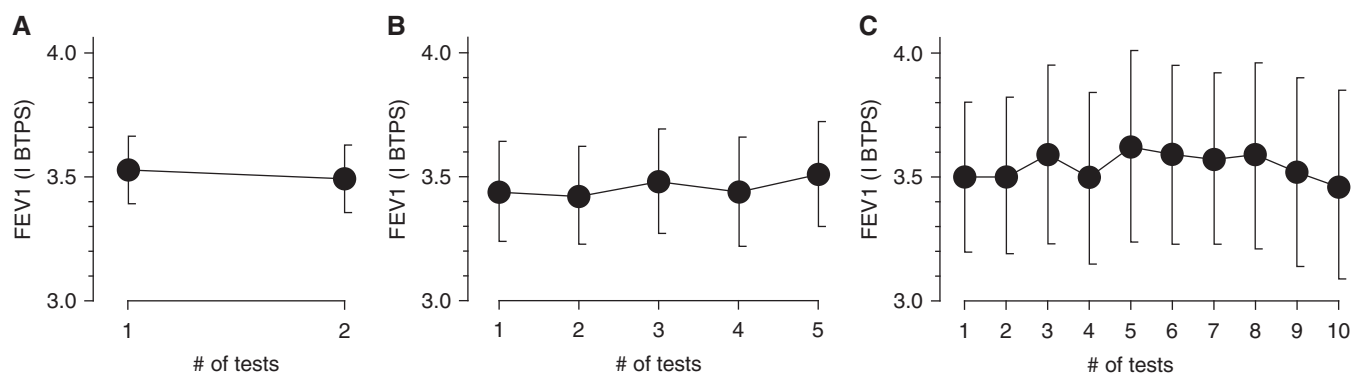


Figure 1. Mean FEV₁ values for subjects who had participated in (A) at least 2 tests (n = 111), (B) at least 5 tests (n = 54), or (C) at least 10 tests (n = 21).

allergen, plus or minus various therapeutic interventions, during the course of that particular asthma study. An appropriate washout period was employed before commencement in the next study. Despite this large number of provocations with methacholine and allergen, these subjects did not exhibit any decline in lung function, as reflected by measurements of FEV₁ made weeks after the challenges. This suggests that the reported markers of airway remodeling in airway biopsies after methacholine bronchoconstriction (1) may be transient and not associated with a lasting decline in lung function or increases in airway hyperresponsiveness.

Irreversible airflow obstruction occurs early in individuals with asthma. In birth cohort studies, a deficit in the FEV₁ or the FEV₁/FVC ratio was identified the first time these measurements were made, at 5 and 9 years of age (4, 5). There was no rapid subsequent decline when these children were monitored into adult life. This suggests that airways are more susceptible to the development of irreversible airflow obstruction early, and that mechanisms develop that limit this progression in most individuals with asthma, despite repeated episodes of bronchoconstriction.

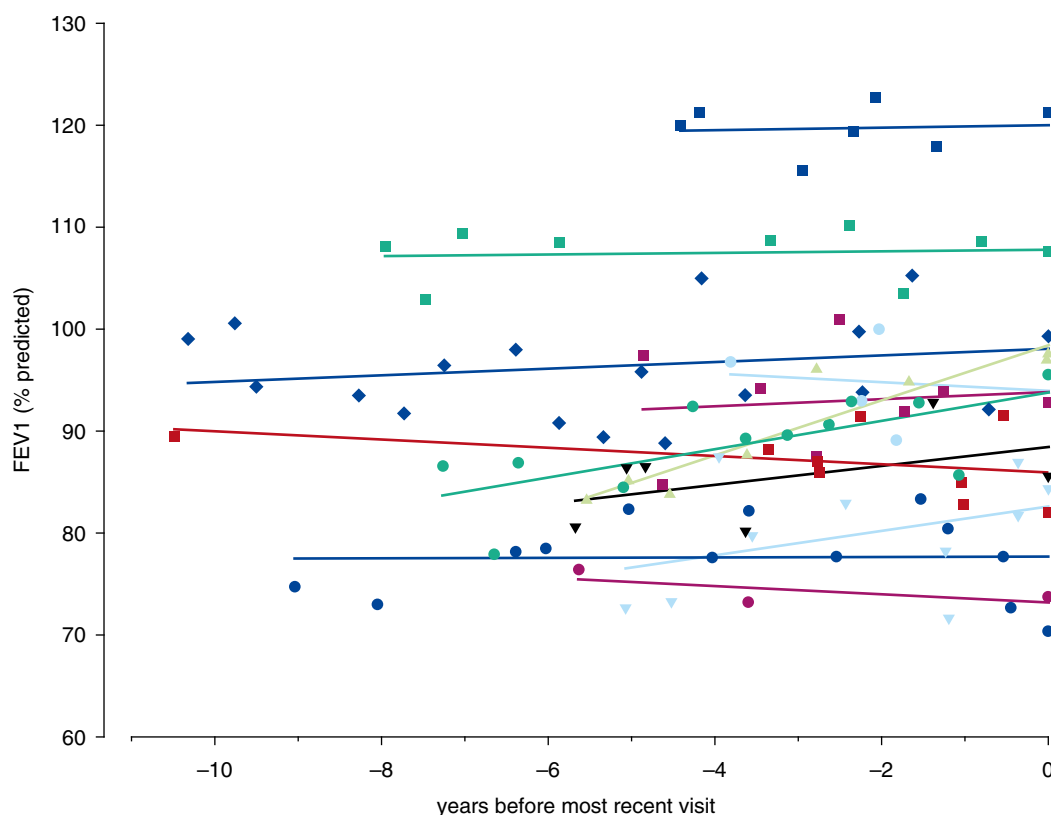


Figure 2. FEV₁ values (% predicted) for all subjects who participated in our studies for at least 3.5 years. Each subject is represented by a unique symbol/color. Linear regression for each individual (colored lines) was performed to evaluate changes over the course of the repeated challenges. Plots were synchronized by defining their last visit as $t = 0$.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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