Changes in FVC During Methacholine-Induced Bronchoconstriction in Elderly Patients With Asthma*

Bronchial Hyperresponsiveness and Aging

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Study objective: We evaluated whether aging may produce changes in bronchial hyperresponsiveness, risk of enhanced bronchoconstriction, and changes of bronchoconstriction perception.
Setting: Each subject underwent a methacholine bronchial challenge. Methacholine challenge was stopped when one of the following conditions occurred: (1) plateau of bronchoconstriction; (2) decrease of $FEV_1 > 40\%$; (3) FEV_1 drop below 1 L; or (4) excessive respiratory discomfort. Methacholine dose-response curves were plotted both for FVC and FEV_1. The provocative dose of methacholine causing a 20% decrease in FEV_1 with respect to baseline (PD_{20}) and the fall in FVC (ΔFVC) at PD_{20} were computed. The Borg scale was used for scoring the perception of respiratory discomfort.
Patients: We compared 17 young asthmatic patients (aged 22 to 45 years) with 17 older asthmatic patients (aged 63 to 78 years) selected on the basis of similar baseline pulmonary function and disease duration.
Results: No significant between-group difference was found in PD_{20} and in plateau development. Conversely, ΔFVC was significantly higher in the older group (mean ± SD, 15.5 ± 3.9% vs 11.6 ± 5.5% in younger patients). In addition, ΔFVC showed a positive linear relationship with age (p = 0.0026). Elderly subjects were less aware of bronchoconstriction during the methacholine challenge (p = 0.04).
Conclusions: In elderly patients with asthma having comparable pulmonary function and disease duration, bronchial responsiveness is not different from that observed in younger asthmatic patients. Nevertheless, in such patients, an age-related tendency to an enhanced bronchoconstriction and a reduced perception of the degree of bronchoconstriction exist.
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Key words: aged; aging; asthma; bronchial hyperreactivity

Abbreviations: ANCOVA = analysis of covariance; ATS = American Thoracic Society; DRS = dose-response slope; FEV_1rev = degree of FEV_1 reversibility; ΔFEV_1 = percentage of decay of FEV_1; ΔFVC = fall in FVC; PD_{20} = provocative dose of methacholine causing a 20% decrease in FEV_1 with respect to baseline; PD_{40} = provocative dose of methacholine causing a 40% decrease in FEV_1 with respect to baseline

In a previous retrospective study, performed in a selected group of nonsmoking healthy subjects, it has been reported that age *per se* has a significant effect on the response to methacholine in bronchial provocation tests.[1] In fact, in that study, the oldest subjects, as well as youngest ones, showed a higher bronchial reactivity. Similar results were also obtained by Connolly et al,[2] who found an increased bronchial responsiveness in elderly asthmatic patients, coupled to a blunted perception of the degree of bronchoconstriction. In the latter study, however, the elderly group showed a poorer functional condition at baseline with respect to the sample of younger patients. If confirmed, this evidence implies that for any given level of exposure to noxious stimuli, elderly asthmatic patients are at a higher risk of airway narrowing.

Moreover, the aging lung may undergo various degrees of change in structure and function, including loss of elastic support to airways and hyperinflation.[3] Since elastic recoil may be a limiting factor for the maximum decrease in airway caliber during bronchoconstriction,[4] the age-related loss in lung elasticity may result in an enhanced bronchoconstriction during acute asthma episodes.

During a bronchial methacholine challenge, the fall in FVC (ΔFVC) at the provocative dose of methacholine causing a 20% decrease in FEV_1 with respect to baseline (PD_{20}) has been proposed as an indirect index of gas trapping and, therefore, an expression of the risk of excessive airway narrowing.[5] In the present study, in two samples of asthmatic patients of different ages but showing similar functional baseline conditions and disease durations, we evaluated whether aging is associated with (1) an increase in the degree of nonspecific bronchial hyperreactivity; (2) a higher risk of enhanced bronchoconstriction, as expressed by the ΔFVC at PD_{20}; and (3) any change in perception of the degree of bronchoconstriction.

Table 1—Anthropometric, Baseline Pulmonary Function, and Disease Characteristics of the Two Study Groups*

Characteristics	Group A (n = 17)	Group B (n = 17)
Age, yr	33.2 (22–45)	71 (63–78)
Male/female gender, No.	4/13	9/8
Height, cm	163.7 ± 11.1	157.9 ± 8.1
$FEV_{1 rev}$,† % of predicted	9.0 ± 9.4	11.9 ± 10.4
Baseline FEV_1, % of predicted	101.5 ± 15.7	93.7 ± 25.3
Baseline FVC, % of predicted	113.8 ± 15.6	117.6 ± 21.5
FEV_1/FVC ratio, absolute %	77.1 ± 9.3	62.8 ± 10.4
Disease duration, yr	11.4 ± 9.3	15.0 ± 5.9
Positive/negative skin prick test results, No.	15/2	8/9

*Data are presented as mean ± SD or mean (range) unless otherwise indicated. None of the differences were significant, with the exception of age (following inclusion criteria), positivity to skin prick tests (χ^2, p = 0.01), and FEV_1/FVC ratio (p = 0.0002).
†Percentage change in FEV_1 with respect to predicted value after administration of salbutamol, 200 μg.

Materials and Methods

Subjects

Seventeen young asthmatic patients (aged 22 to 45 years; group A) and 17 elderly asthmatic patients (aged 63 to 78 years; group B) were studied after informed consent was obtained. All patients were affected by bronchial asthma, as defined according to the American Thoracic Society criteria.[6] All were nonsmokers at the time of the study. Allergen skin tests were performed by the prick test method. Subjects with positive findings for one or more of the most common allergens (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, grass pollen, parietaria, molds, dog and cat dander, olive) were considered as atopic.

The two groups were selected on the basis of comparable pulmonary function, as defined by FEV_1 expressed as the percentage of predicted value,[7] and of comparable disease duration (Table 1). All the subjects were free of respiratory tract infection or significant allergen exposure for at least 6 weeks before the study. All were in clinically stable condition at the time of study. Caffeine-containing foods and beverages were withheld for 8 h prior to testing. Short-acting and long-acting β_2-agonists were discontinued for 24 h and 48 h, respectively, prior to testing. No subject was receiving theophylline or systemic steroids. Treatment with inhaled corticosteroids and cromolyn sodium was withheld for at least 4 weeks before the study. The study was approved by the institutional ethical committee.

Methacholine Challenge Tests

All tests were done at the same time of day (9 AM to 11 AM). Each subject underwent a methacholine challenge test by using an ampul-dosimeter (Mefar Elettromedicali; Bovezzo, Italy) delivering particles with an aerodynamic mass median diameter ranging from 1.53 to 1.61 μm. An inspiratory effort activated for 0.5 s a solenoid valve that delivered 5 μL of solution. After a

saline solution control, methacholine was administered in doubled increasing amounts. The starting dose of methacholine was 2 μg. All the accepted functional data were obtained from FVC maneuvers performed according to ATS criteria[8] and using a computerized water-sealed spirometer (Biomedin; Padua, Italy), allowing the on-line check of compliance with ATS criteria. All FVC and FEV_1 measurements were recorded about 2 min after each inhalation.[9] The FVC and FEV_1 measured after saline solution control were assumed as baseline values. The challenge was stopped when one of the following conditions occurred: (1) a plateau of bronchoconstriction, as shown by a FEV_1 variation within 5% for three successive doubling doses of methacholine; (2) a decrease of $FEV_1 > 40\%$ with respect to baseline value; (3) a FEV_1 drop below 1 L; or (4) respiratory discomfort inducing the subjects to stop the test. On a different day, at the same time, all the subjects underwent a bronchodilatation test by inhalation of salbutamol, 200 μg. The degree of FEV_1 reversibility (FEV_1rev) was assessed as the percent of change in FEV_1 with respect to the predicted value. The Borg scale was used for the scoring of the perception of respiratory discomfort during the methacholine challenge.

Data Analysis

For each administered methacholine dose, the percentage decay of FEV_1 (ΔFEV_1) and FVC (ΔFVC), respectively, was computed. The cumulative PD_{20} and the cumulative provocative dose of methacholine causing a 40% decrease in FEV_1 with respect to baseline (PD_{40}) were calculated. The PD_{20} and PD_{40} were computed by interpolation on the line connecting the methacholine cumulative doses immediately preceding and following the 20% and 40% falls. On all the data points of each dose-response curve, we also computed a dose-response slope (DRS) of the relationship between percentage of FEV_1 fall with respect to baseline and the cumulative methacholine dose. Since the distributions of PD_{20} were markedly skewed, in order to perform linear regression analysis we used the natural log transformation of PD_{20}. The ΔFVC values at PD_{20}[5] and at PD_{40}

were also computed. The presence or absence of a plateau was noticed. The perception of bronchoconstriction was evaluated as the difference in the score of the Borg scale measured after the last administered dose and that immediately before the baseline measurement.

Statistical analysis was performed by the use of analysis of variance and frequency distribution tables (χ^2). Since the distribution of PD_{20}, PD_{40}, and Borg score was highly skewed in both groups, for statistical comparison the Mann-Whitney U test for nonparametric data was used. Correlations among variables were investigated by the use of simple and multiple linear regression analysis. The difference between slopes was evaluated by the analysis of covariance (ANCOVA). All computations were performed using StatView (Abacus Concepts; Berkeley, CA) and Systat (Systat; Evanston, IL) software packages. A probability level of $p = 0.05$ was selected as statistically significant.

Results

Anthropometric, baseline pulmonary function, and disease duration characteristics of the two study groups are presented in Table 1. None of the listed variables (height, weight, baseline FEV_1, and FVC, disease duration, and FEV_1rev) was significantly different in the two study groups. Conversely, the FEV_1/FVC ratio was significantly lower in group B than in group A.

Smoking habit distribution was not statistically different between groups (χ^2): 12 lifelong nonsmokers and 5 former smokers in group A, and 10 lifelong nonsmokers and 7 former smokers in group B. Concerning the atopic status, we found a significant difference (χ^2, $p = 0.01$) in terms of response to prick test: 15 positive responses and 2 negative responses in group A, and 8 positive responses and 9 negative responses in group B.

In Table 2, we report the results relevant to bronchial challenges. All the patients showed a wide range of responses in terms of PD_{20} and PD_{40}. The between-group differences in PD_{20} and PD_{40} were not statistically significant, and the same result was obtained using the DRS. Similarly, no difference was found when the plateau development was investigated (2 of 17 subjects showing a plateau in the

methacholine dose-response curve in group A, and 3 of 17 subjects in group B; Fig 1). On the overall sample, we did not find any significant difference in PD_{20}, PD_{40}, and DRS on the basis of skin test positivity. Conversely, as concerns ΔFVC at PD_{20}, the values obtained in group B were significantly higher (mean ± SD, $11.6 \pm 5.5\%$ in group A vs $15.5 \pm 3.9\%$ in group B, $p = 0.03$, Fig 2). In addition, the individual values of ΔFVC at PD_{20} were linearly correlated with age ($p = 0.0026$). The between-group difference in ΔFVC was maintained also at the PD_{40} level (ΔFVC at PD_{40} was $27.1 \pm 7.1\%$ in group A and $32.0 \pm 4.9\%$ in group B; $p = 0.045$; Fig 2). The relationships between ΔFVC and ΔFEV_1 along dose-response curves showed high regression coefficients (R^2 values were 0.785 in group A and 0.876 in group B); the slopes were 0.66 in group A and 0.79 in group B, with the difference being significant (ANCOVA, $p = 0.002$; Fig 3).

The analysis of scores obtained by the evaluation of dyspnea sensation during the methacholine challenges showed significantly higher values in group A ($p = 0.026$; Table 2). No relationship was found in univariate analysis between the natural log transformation of PD_{20} (as dependent variable) and age, disease duration, and baseline FEV_1 as independent ones. The multiple linear regression analysis using all the latter as independent variables did not improve the R^2 value.

Discussion

The results of the present study point out that in adult asthmatic patients of different ages, when disease duration and baseline pulmonary function are comparable, the degree of nonspecific bronchial hyperresponsiveness, as expressed by conventional parameters, is not significantly different. However, elderly asthmatic patients undergo larger falls in FVC, suggesting a tendency to more marked increases in lung inflation and, possibly, a risk of

Table 2—Results of Methacholine Challenge*

Variables	Group A	Group B	p Value
PD_{20}, μg	69.3 (1.6–540)	94.0 (1.8–1,500)	NS
PD_{40}, μg	220.4 (3.2–1,745)	321.2 (5.9–3,250)	NS
DRS†	0.081 (0.02–12.33)	0.097 (0.01–5.62)	NS
Plateau present/absent in the dose-response curve, No.	2/15	3/14	NS
Borg scale score‡	1.0 (0.5–5)	0.5 (0–5)	0.026§

*Data are presented as geometric mean (range) or No. unless otherwise indicated. NS = not significant.
†Slope of the relationship between percentage of FEV_1 fall with respect to baseline and cumulative methacholine dose, given as median (range).
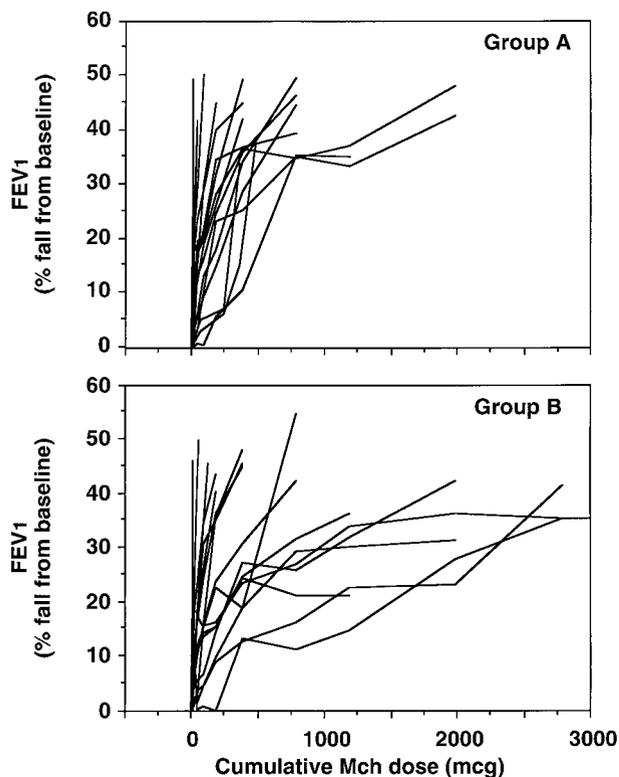‡Data presented as median (range).
§Mann-Whitney U test.

FIGURE 1. Dose-response curves for each asthmatic subject. *Upper panel*: group A. *Lower panel*: group B. Mch = methacholine.

FIGURE 3. Relationship between the ΔFVC and ΔFEV$_1$ obtained plotting the individual points of dose-response curves. The linear regression lines, computed separately for group A and group B, were both significant. The slopes were 0.66 for group A and 0.79 for group B. The difference between slopes was significant (ANCOVA, p = 0.002).

enhanced bronchoconstriction. This risk is aggravated by a reduced perception of bronchoconstriction.

In a population of healthy adult subjects aged 20 to 60 years, Malo et al[10] failed to demonstrate a significant age effect on the response to methacholine challenge. Similarly, Renwick and Connolly[11] found only a weak increase in bronchial responsiveness in elderly subjects in an age-stratified random population sample. Moreover similar negative results
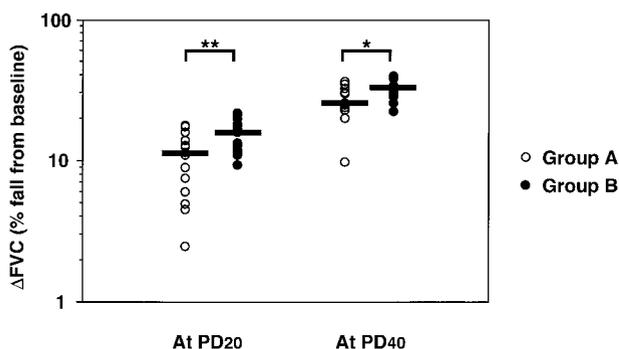
were obtained in cross-sectional investigations.[12,13] Conversely, in nonsmoking healthy individuals aged 5 to 86 years, Hopp et al[1] found that age *per se* had a significant effect on the methacholine response. Other studies,[14–16] based on general population surveys and cross-sectional investigations, showed an increased bronchial responsiveness in older subjects. These controversies could be due to the low percentage of elderly subjects participating in various studies or to the different selection criteria of samples that may include a variable proportion of smokers or of respiratory patients.

The evidence relevant to asthmatic patients is even more scanty. Connolly et al,[2] in an article evaluating the awareness of induced bronchoconstriction, found a higher bronchial responsiveness in elderly subjects. However the baseline pulmonary function conditions were poorer in older subjects. Because the prechallenge pulmonary function is inversely related to bronchial responsiveness,[17,18] in our study we kept the baseline functional conditions comparable. Mean baseline FEV$_1$ values were 102% of predicted and 94% of predicted in group A and group B, respectively.

Concerning disease duration, previous reports showed that asthma duration may cause changes in characteristics of airflow obstruction. In fact, Braman et al[19] reported that patients with long-standing asthma showed a lower acute response to the inhalation of a bronchodilator. Similarly, in a previous report,[20] we showed that in young asthmatic patients the maximum long-term response to bronchodilator treatment was significantly lower in subjects with long-standing asthma. Thus, we selected two groups

FIGURE 2. Individual values of percentage of ΔFVC at PD$_{20}$ and at PD$_{40}$, separately for group A and group B. Bars indicate group means. The vertical axis is expressed in logarithmic scale. ** = p = 0.03; * = p = 0.045.
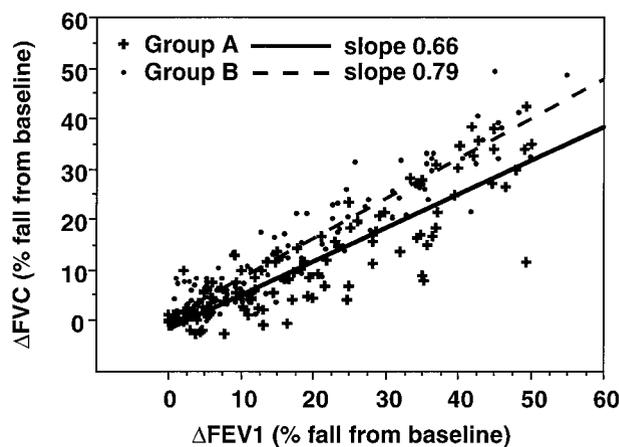
with comparable mean durations of illness. As a consequence of selection criteria, the two asthmatic patient samples were different in the age of disease onset. This may easily explain the differences in the prevalence of skin test reactivity, which is less frequent in asthma developed in elderly.[21]

In our younger group, we found largely scattered PD_{20}, PD_{40}, and DRS values, but similar results were obtained also in the group of aged asthmatic patients. This suggests similar conditions of muscle reactivity, and this interpretation is further supported by the lack of significant difference between groups as concerns the acute bronchodilator response, as previously shown.[20] Similarly, previous results showed that elderly asthmatic patients have similar bronchial lability[22] as evaluated by measures of peak expiratory flow variability.[23]

Recently, the ΔFVC measured at PD_{20} has been demonstrated to be an indirect index of gas trapping and therefore of excessive airway narrowing, whereas PD_{20} measures only the ease of bronchoconstriction[5] and a plateau in the dose-response curve only suggests the presence of some protective mechanisms.[4,24] Due to its clinical implications, the excessive bronchoconstriction appears as the most crucial abnormality in bronchial asthma. We found a significant difference in ΔFVC at PD_{20}, which was greater in group B. This difference was still maintained when looking at ΔFVC fall at PD_{40}. This phenomenon is age related, and between-group differences exist as shown by the difference in the slopes of the relationship of ΔFVC vs ΔFEV$_1$ (Fig 3). These findings suggest that in elderly asthmatic patients, a tendency to enhanced bronchoconstriction may be present.

The interpretation of these results may only represent a matter of speculation. A possible explanation of our findings could be founded on the assumption that the aging lung may undergo various degrees of changes in structures and functions.[3] These age-related changes probably add their effects to the loss of elastic support to airways present in asthma patients[25] producing an age-related tendency to gas trapping and exposing elderly asthmatic subjects to the risk of enhanced bronchoconstriction. The possible role of the loss of elastic support to the airways is also suggested by the lower baseline FEV$_1$/FVC ratio in group B. This was due to a lower (even though not significantly) baseline FEV$_1$ and to a higher (again not significantly) FVC in group B. Therefore, given the lack of significant difference in baseline FEV$_1$, we hypothesize that the difference in FEV$_1$/FVC ratio may be partly related to the loss of elastic support that underlies the observed increase in ΔFVC at PD_{20}.

The risk of enhanced bronchoconstriction is made even more severe because of the evidence of an impaired perception of bronchoconstriction in the elderly. This is suggested by a significant lower Borg scoring in group B during the methacholine challenge, according to the results obtained by Connolly et al[2] in asthmatic subjects of different age. Since elderly subjects are more prone to muscle weakness and fatigue, it may be hypothesized that the reduction in FVC may be a consequence of progressive shortening in expiration leading to incomplete emptying of the lungs. However, this is not the case, since the compliance with ATS criteria, including the occurrence of an expiratory plateau, was checked in all cases.

In conclusion, our results suggest that in elderly asthmatic patients, when both pulmonary function and disease duration are comparable, the degree of bronchial responsiveness is not different from that of younger asthmatic patients. Nevertheless, in patients affected by bronchial asthma, an age-related tendency to an enhanced bronchoconstriction and to a reduced perception of the degree of bronchoconstriction exists. This could suggest the need of a more careful and objective monitoring of asthma in this age group.

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