Lung Function Decline in Bronchial Asthma*

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Study objective: We evaluated the longitudinal changes in lung function and the factors associated with FEV1 changes over time in a sample of asthmatic subjects.

Setting: FEV1 measures were recorded every 3 months over a 5-year follow-up period. To compare all subjects independently of body size, FEV1 values were normalized for the subject’s height at the third power. We evaluated the possible effect of age, baseline FEV1, disease duration, and FEV1 variability on the rate of change of FEV1.

Patients: We studied 142 subjects with asthma diagnosed on the basis of validated clinical and functional criteria.

Results: FEV1 showed a linear decay with aging in each subject. For a subject 1.65 m in height, the median overall FEV1 decay was 40.9 mL/yr. FEV1 decay slopes were significantly influenced by age and sex, being steeper in younger male subjects. A significant interaction was found between age and baseline FEV1: the FEV1 decay was significantly higher among younger asthmatics with a poorer baseline functional condition. A longer disease duration was associated with a lower FEV1 slope. FEV1 variability was strongly associated with an increased rate of FEV1 decline.

Conclusions: FEV1 decline in patients with bronchial asthma is significantly influenced by baseline FEV1, disease duration, and FEV1 variability. Moreover, the rate of FEV1 decline seems to increase in younger subjects only when the baseline function is poorer.

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Key words: asthma; forced expiratory volume; lung function decline

Abbreviations: ANOVA = analysis of variance; BMI = body mass index; baseline FEV1% = FEV1 measured at the first evaluation and defined as the baseline value and expressed as a percentage of the predicted value; FEV1/Ht3 = FEV1 data normalized for the subject’s height at the third power; FEV1rev,% = FEV1 reversibility; ln = natural logarithm

Conflicting results have been reported regarding the influence of bronchial asthma on the rate of decline of lung function: the data available indicate rates of decline in FEV1 ranging from a value very close to normal1 to a value similar to those expected in COPD.2 More recent studies have evaluated FEV1 decline in large population samples,3,4 and the results suggest that asthma has a significant impact on lung function decline, although not as great as COPD. These results could be partly due to differences in experimental methods as well as to limitations in the accuracy of the diagnosis. In fact, in the cited studies, the diagnosis of asthma was based on subjects’ responses to a questionnaire, a method with a possible diagnostic bias that cannot be underestimated.5 The present study was performed on a sample of patients with asthma diagnosed on the basis of validated clinical and functional criteria. The aims were as follows: (1) to evaluate the longitudinal changes in lung function in patients with asthma during a 5-year functional survey, and (2) to identify factors that could affect the rate of change in lung function over time.

Materials and Methods

One hundred forty-two asthmatic outpatients (55 men and 87 women; age range, 20 to 64 years; Table 1) were enrolled for the study. All of the patients attended the asthma clinic of a teaching hospital, and all reported a personal history of bronchial asthma, with a diagnosis confirmed by clinical and functional assessment as defined by American Thoracic Society criteria.6 All of the patients were lifelong nonsmokers. Allergen skin tests were
Table 1—Anthropometric, Clinical, and Pulmonary Function Characteristics at Enrollment*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male Patients (n = 55)</th>
<th>Female Patients (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>40.1 ± 12.6</td>
<td>42.0 ± 12.3</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.71 ± 0.06</td>
<td>1.57 ± 0.07</td>
</tr>
<tr>
<td>BMI</td>
<td>25.8 ± 3.3</td>
<td>26.0 ± 5.1</td>
</tr>
<tr>
<td>Age of disease onset, yr</td>
<td>30.9 ± 15.1</td>
<td>31.1 ± 13.7</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>5.5 (1-44)</td>
<td>8.8 (1-45)</td>
</tr>
<tr>
<td>Positive/negative skin-prick test results, No.</td>
<td>36/19</td>
<td>55/32</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or median (range) unless otherwise indicated. None of the differences were significant (ANOVA or χ² test) between male and female subgroups, with the exception of disease duration (p < 0.03, Mann-Whitney U test).

performed by the skin-prick test method with an inhalant allergen panel for Southern Italy (Lofarma S.p.A; Milano, Italy). Atopy was defined as positive reactions of ≥ 5 mm for one or more of the tested allergens.

All the subjects were followed up during a 5-year follow-up period, and they underwent spirometric evaluations every 3 months. On each occasion we recorded FVC and FEV₁, Moreover, at the enrollment, an immediate bronchodilatation test was performed by the inhalation of salbutamol, 200 µg. Acute responsiveness to bronchodilator was expressed as FEV₁ reversibility (FEV₁rev, %), using the following formula:

$$\text{FEV}_{1\text{rev}} = \frac{\text{FEV}_{1\text{postBD}} - \text{FEV}_{1\text{preBD}}}{\text{FEV}_{1\text{pred}}} \times 100$$

where FEV₁postBD and FEV₁preBD are FEV₁ values recorded before and 20 min after the administration of salbutamol, respectively, and FEV₁pred is the individual predicted FEV₁.

Once enrolled, each patient was admitted to pharmacologic treatment according to the suggestions of the British Thoracic Society. All functional measurements were performed following American Thoracic Society recommendations and using a computerized water-sealed spirometer (Biomedin; Padua, Italy). The FEV₁ measured at the first evaluation was defined as the baseline value and expressed as a percentage of the predicted value (baseline FEV₁bs).

During the 5-year follow-up, we performed a functional evaluation every 3 months; thus, we recorded 20 measurements for each subject. The best FEV₁ measure in each 6-month period was selected for analysis, and individual FEV₁ decay slopes were computed on 10 FEV₁ measurements (ie, two per year) in the 5-year follow-up.

In order to compare all the subjects independently of body height, FEV₁ data were normalized for the subject’s height at the third power (FEV₁/height³). For each subject, normalized data points were plotted against age in years (and year fractions) at the time of each measurement.

For each subject, the relationships between FEV₁ as dependent variable and age as the independent variable were treated by linear regression analysis to obtain individual slopes of FEV₁ vs time (slope FEV₁/height³). Due to their skewed distribution, the slope FEV₁/height³ values were expressed as natural logarithm (ln) [ln slope FEV₁/height³] to perform statistical analysis. The individual ln slope FEV₁/height³ values were tested against the investigated factors: sex, age (< 43 years and ≥ 43 years), the median value of our population sample: body mass index (BMI) (< 25 and ≥ 25), the median value of our population sample; baseline FEV₁ (< 80% and ≥ 80% of predicted); age of disease onset (< 31 years and ≥ 31 years, the median value of our population sample); disease duration (< 15 years and ≥ 15 years, 15 years being the 75th percentile of our population sample)²⁵; and atopic status.

To evaluate the effect of bronchial reactivity on longitudinal changes in FEV₁, we computed an index of FEV₁ variability for each subject, using the following formula¹¹:

$$\text{FEV}_{1\text{pred}} = \frac{\text{FEV}_{1\text{max}} - \text{FEV}_{1\text{min}}}{\text{FEV}_{1\text{pred}}} \times 100$$

where FEV₁max and FEV₁min are the maximum FEV₁ and the minimum FEV₁ recorded during the first year of follow-up, respectively, and FEV₁pred is the individual predicted FEV₁.

Correlation between variables was investigated using simple linear regression analysis. Differences between means and the interactions between different factors were evaluated by the one-way and two-way analysis of variance (ANOVA). The differences between nonparametric variables were evaluated by the Mann-Whitney U test. The difference in the frequency distribution of variables was evaluated by χ² test. All computations were performed using Systat software (Systat; Evanston, IL). A probability level of p < 0.05 was selected as statistically significant.

RESULTS

Patients’ anthropometric, clinical, and pulmonary functional characteristics at enrollment are presented in Table 1. Age, FEV₁, FVC, FEV₁/FVC ratio, FEV₁rev, %, age of disease onset, BMI, and atopic status were not significantly different between male and female subgroups at enrollment. Disease duration was significantly higher in female patients.

Decay in Lung Function

All FEV₁/height³ slopes showed negative values. The median overall FEV₁/height³ decay slope, computed on the whole population sample, was −0.0091 L/m³/yr, equivalent to a FEV₁ loss of 40.9 mL/yr, computed for a subject of 1.65 m in height (the median height of our population sample).

Figure 1 presents the FEV₁/height³ slope values, separating male and female patients. The median values for individual FEV₁ slopes were as follows: −0.0059 L/m³/yr (range, −0.0003 to −0.0460 L/m³/yr) and −0.0092 L/m³/yr (range, −0.0005 to −0.0486 L/m³/yr) for male and female subgroups, respectively. The FEV₁/height³ slope values were not significantly different between male and female subgroups (Mann-Whitney U test).

Factors Affecting Lung Function Decay

In the whole sample, we did not find a significant effect of age on FEV₁/height³ decay slopes. Nevertheless, the slopes were significantly steeper in younger...
men than in older men, while no difference was found among women (Fig 2).

In the total sample, the baseline FEV$_{1\%}$ did not significantly influence FEV$_1$ decay, but when we evaluated the interaction between the effects of baseline FEV$_{1\%}$ and age groups, the FEV$_1$/Ht$^3$ decay was significantly higher among younger asthmatics with baseline FEV$_{1\%}$ < 80% predicted than among older asthmatics (two-way ANOVA, *p* < 0.03). Age did not produce any effect on subjects with a baseline FEV$_{1\%}$ ≥ 80% of predicted (Fig 3).

In the subgroup with a disease duration < 15 years, the FEV$_1$/Ht$^3$ decay slopes were significantly steeper than in the remaining subjects (*p* < 0.03; Fig 4). Disease duration was not associated with age groups ($\chi^2$).

FEV$_1$ variability had a strong effect on lung function decline: subjects with FEV$_1$ variability ≥ 15% (sample median) showed a significantly higher FEV$_1$/Ht$^3$ decay slope (ANOVA, *p* < 0.0001; Fig 5). The correlation between FEV$_1$ decay slope and acute responsiveness to bronchodilator at the enrollment was not significant.

The correlations between FEV$_1$/Ht$^3$ decay slope as dependent variable and BMI and age of disease onset as independent variables were not significant. Similarly, the presence or absence of atopy did not show any effect on FEV$_1$ decay.

**DISCUSSION**

The present study was carried out on 142 lifelong nonsmoking, adult, asthmatic outpatients with a well-defined diagnosis of bronchial asthma, who were submitted to a 5-year follow-up with pulmonary functional evaluations performed every 3 months. Our results point out that in asthmatics, the median unadjusted FEV$_1$ decay over time, computed for a subject 1.65 m in height, was 40.9 mL/yr, with no significant difference between male and female patients. We found that the FEV$_1$ decline was 38% more pronounced for male patients and 65% for
female patients when compared to the values obtained from a suitable reference population\textsuperscript{12} (Table 2).

Differences in Age, Baseline FEV\textsubscript{1}, Disease Duration, and FEV\textsubscript{1} Variability Were Associated With Changes in FEV\textsubscript{1} Decay Over Time

In our study, the magnitude of FEV\textsubscript{1} decline is very close to that observed by Lange and coworkers\textsuperscript{4} in the largest survey ever performed on FEV\textsubscript{1} decay in patients with asthma. These authors reported an overall unadjusted decline in FEV\textsubscript{1} of 38 mL/yr in asthmatics, as compared with 22 mL/yr in subjects without asthma. Conversely, Peat and coworkers\textsuperscript{9} found a FEV\textsubscript{1} decay equal to 50.5 mL/yr for a male patient 1.70 m in height during their 18-year follow-up. In that study, 92 asthmatic patients underwent four to seven spirometric evaluations during the observation, and the functional decay was found to be significantly higher with respect to the reference population.

It has been suggested that the differences among studies relevant to longitudinal functional evaluations may be due to the following: (1) incorrect diagnosis (healthy status vs asthma vs COPD) due to limitations of selected methods (eg, self-reported diagnosis, questionnaire); (2) incorrect inclusion of functional values collected during exacerbations\textsuperscript{5}; (3) inclusion of few functional measures for each subject in a long follow-up (the “learning” effect causes higher values in functional evaluations producing, in turn, an underestimation of decline); and (4) variable effect of pharmacologic control of bronchoconstriction over time. In our study, we tried to overcome these potential problems, as follows: (1) by evaluating subjects with ascertained diagnosis based on personal history and on clinical and functional evaluation; (2) by increasing the number of functional measurements in the follow-up period and thus minimizing the “learning” effect; and (3) by selecting the best measure in each 6-month period, to decrease the risk due to asthma exacerbations or to changes in disease control over time.

In our study, asthma diagnosis was both clinical and functional, and multiple measurements of lung function were performed. Individual decay slopes were computed on a total of 10 measurements obtained during a 5-year follow-up; this protected the results against the regression toward the mean (ie, the dependence of slope value on the starting point), and produced a more reliable value of decay rate. Moreover, we excluded both current and former smokers from the sample, thus eliminating any effect of smoking on lung function decline.

We did not find any difference in lung function decay between male and female subgroups. Conversely, an accelerated functional decline was found in younger male asthmatics, as demonstrated by the significant association between FEV\textsubscript{1} decay slope and age in the male subgroup (Fig 2). With regard to the influence of age on lung function decay in asthma, conflicting results have previously been reported. Peat et al\textsuperscript{10} did not find any influence of age on the functional decline over several years in asthma. Conversely, in a more recent article, aging was found to be associated with a steeper decline in FEV\textsubscript{1}.

These contradictory results concerning the relationship between lung function decay in asthma and age and baseline pulmonary function could be explained on the basis of differences in age and the clinical features of patients in previous studies. In fact, when our data were analyzed on the basis of interaction between age and functional status at the enrollment, we found that younger subjects with a baseline FEV\textsubscript{1}\% < 80\% of predicted showed an increased FEV\textsubscript{1} decay with respect to older subjects (Fig 3). These findings suggest that in older asthmatics the rate of pulmonary function loss may slow

\begin{table}[h]
\begin{center}
\begin{tabular}{|c|c|c|}
\hline
Patients & Present Study & Reference Values\textsuperscript{1} \\
& FEV\textsubscript{1}, mL/yr & FEV\textsubscript{1}, mL/yr \\
\hline
Men & 40.0 & 29 \\
Women & 41.3 & 25 \\
\hline
\end{tabular}
\end{center}
\caption{Overall FEV\textsubscript{1} Rate of Decline Obtained From the Median Values of the Present Study, Compared to Normal Lung Function Values for FEV\textsubscript{1} Decline With Age Obtained From a Suitable Reference Population\textsuperscript{8}}
\end{table}

\textsuperscript{8}FEV\textsubscript{1} decline values were separately calculated for a male patient and a female patient 1.65 m in height.

\textsuperscript{1}From Quanjer.\textsuperscript{12}
down. In fact, in a previous study we found that older asthmatics show a lower effect of disease duration on maximum achievable bronchodilatation.\textsuperscript{11} Therefore, we suggested that aging \textit{per se}, unlike the duration of disease, may lower the intensity of the events of remodeling that characterize chronic asthma and thus produce a slower rate of decline in lung function.

Moreover, we found that after a long disease duration (\geq 15 years), the rate of decline of lung function may decrease; it is noteworthy that in our sample, classes of disease duration and age are not associated, suggesting that the two factors may independently influence lung function. Similar results were obtained by Ulrik and Lange,\textsuperscript{3} who showed that men with late-onset asthma presented an increased \textit{FEV}_1 decline with respect to subjects with early-onset asthma. Ulrik\textsuperscript{14} raised the question of whether an increased decline in lung function in bronchial asthma may be attributable to the baseline \textit{FEV}_1 value or to disease progression. In our sample, disease duration and baseline \textit{FEV}_1 were not correlated. Moreover, while long disease duration produces a slower \textit{FEV}_1 decline, a poorer baseline \textit{FEV}_1 produces an increased rate of decay in younger subjects. For this reason, we suggest that both the variables may play an independent role in influencing the pulmonary function decline in asthmatic patients.

Nonspecific bronchial responsiveness has been demonstrated to be a significant risk factor for an accelerated longitudinal \textit{FEV}_1 decline.\textsuperscript{15,16} Moreover, Ulrik et al\textsuperscript{13} observed that a higher \textit{FEV}_1,\textit{rev},\% is associated with a steeper lung function decline in adult asthmatics. In our study, the acute response to bronchodilator was not correlated to the individual slope of \textit{FEV}_1 decay. This lack of significance may be explained on the basis of an underestimation of acute bronchodilatation when a marked airway inflammation is present. Consequently, we chose to compute an index to represent longitudinal changes in lung function. Thus, we evaluated the maximum lung function variability on the basis of the largest change in \textit{FEV}_1 recorded in each subject during the first year of follow-up. \textit{FEV}_1 variability in the first year was the strongest predictor of lung function decline in our population sample. This result supports the hypothesis that a greater variability of pulmonary capacity over time is a marker of poorly controlled asthma, thus significantly affecting the rate of lung function decline. According to previous studies,\textsuperscript{9,17} we found that atopy does not appear to be a determinant of changes in the rate of lung function decay in asthma, suggesting that inflammatory processes in the airways of patients with asthma may run their course irrespective of the subjects' atopic status.

In conclusion, the results of the present study indicate that lung function decline in bronchial asthma is significantly influenced by age, disease duration, and \textit{FEV}_1 variability. Moreover, younger asthmatics seem to present an increased \textit{FEV}_1 decline only when their baseline pulmonary function is poorer.

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