Effect of Age Upon Airway Obstruction and Reversibility in Adult Patients With Asthma

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Objective: In a cross-sectional study we evaluated the effect of aging (separately from that of duration of disease) on airway obstruction and reversibility by comparing two groups of non-smoker patients with asthma.

Methods: We compared two groups of patients: group A, which had 50 subjects (8 men and 42 women) aged 59.7 ± 4.6 years (mean ± SD), and group B, comprised of 51 subjects (19 men and 32 women) who were 35.7 ± 7.4 years old. The groups were selected because of comparable baseline degree of obstruction (FEV₁ % of predicted, 67.8 ± 20.3 in group A; 73.0 ± 19.6 in group B, NS) and duration of the disease (14.0 ± 11.7 years vs 11.2 ± 9.1, NS). Spirometric examination, with a bronchodilator test, was performed and subjects not reaching 85% of predicted were submitted to a 4-week course of inhaled steroids.

Results: Although a higher number of subjects from group B responded to the acute bronchodilator test (p < 0.001), the maximum response achievable with treatment (steroid or bronchodilator) (ΔFEV₁ expressed as the percent of predicted) was not statistically different between groups (12.0 ± 17.5 vs 16.0 ± 23.9). The mean FEV₁ attainable after treatment (ΔFEV₁%PT) was significantly lower in the older group (p = 0.0006). Within groups, the baseline FEV₁% did not correlate with age; it was inversely correlated with the duration of the disease (p < 0.03 and p < 0.01, respectively). In both groups ΔFEV₁ was inversely related with the baseline FEV₁, whereas FEV₁%PT was correlated with the duration of the disease, with a slope nearly doubled in group B (p < 0.001).

Conclusions: Both the process of aging and the prolonged exposure to disease effects are important factors in determining the functional characteristics of chronic asthma: In particular, aging is associated not only with a reduced acute responsiveness to bronchodilators, but also with a reduced slope of the duration-FEV₁%PT relationship that suggests a slowing of the rate of loss of reversibility of uncertain biological meaning. (CHEST 1998; 114:1336–1342)

Key words: aging; airway obstruction; asthma; elderly; functional decline; reversibility

Abbreviation: PT = posttreatment

Epidemiologic evidences suggest that bronchial asthma is not rare in elderly patients.¹ The characteristics of the disease in this age group are determined by the complex interaction of phenomena relevant to areas still covered by a considerable grade of uncertainty. Aging is accompanied by several phenomena (such as undernutrition, decline of immune function, or increased catabolism of extracellular matrix) that influence to some extent structures and functions (such as loss of elastic support to airways, hyperinflation, or relative loss of respiratory muscle strength) involved in the disease process.² In addition, other physiologic age-related phenomena (in particular the reduction of the number, activity of receptors, or both in bronchial smooth muscle)³–⁵ may affect the response to treatments. However, it is not known whether increasing age as an outcome of all these factors, ie, independent of its inevitable likelihood of association with a long duration of the disease, influences the functional condition of patients with asthma and its response to treatment.

The present cross-sectional study was carried out on two groups of patients with asthma of different ages but characterized by comparable duration of...
disease and degree of baseline functional impairment and was aimed at evaluating the effects of aging on the characteristics of functional impairment, with a particular emphasis on the degree of reversibility subsequent to treatment.

MATERIALS AND METHODS

The study was carried out on outpatients attending the asthma clinics of a university hospital. All patients were affected by bronchial asthma, as defined according to the American Thoracic Society criteria.* All were lifelong non-smokers and none of them reported a present or previous history of professional exposure to hazardous airborne substances. The study was approved by the institutional ethical committee; informed consent was obtained from the investigated patients.

Group A included 50 patients aged 53 to 74 years (mean ± SD; 59.7 ± 4.6; 8 men, 42 women); group B included 51 patients aged 14 to 47 years (35.7 ± 7.4; 19 men, 32 women) (Table 1). The two groups were selected because they were not statistically different in duration of disease nor degree of airway obstruction under baseline condition.

All the patients were submitted to a questionnaire evaluating family and personal history, including atopy, age of onset, and course of respiratory symptoms, with a special emphasis on the provoking factors. Both groups were subdivided into subsets characterized by early (> 5 years before the study) and late (≤ 5 years before the study) onset of disease.

The two groups did not differ in terms of prestudy medications (p = 0.12) (Table 2). The medications were discontinued for 24 h and baseline spirometric examination was performed: the baseline FEV₁ was measured and expressed as the percent of predicted value (FEV₁/B%); then an immediate bronchodilatation test was performed using inhalation of salbutamol, 200 µg. Thereafter, all patients not reaching an FEV₁ value higher than 85% of predicted were prescribed a 4-week course of inhaled steroids; in all cases submitted to a stable prestudy treatment, the latter was kept constant throughout the whole study period. After 4 weeks, a new spirometric assessment was performed under the same conditions in all patients. The degree of reversibility (ΔFEV₁/B%) was assessed as the maximum percentage change in FEV₁, with respect to predicted value, expressed as

\[
\frac{\text{FEV₁postBD} - \text{FEV₁baseline}}{\text{FEV₁predicted}} \times 100.
\]

Table 1—Age and Disease Data Relevant to Both Groups

<table>
<thead>
<tr>
<th></th>
<th>Older Group</th>
<th>Younger Group</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>59.7 ± 4.6</td>
<td>35.7 ± 7.4</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Age of disease onset, yr</td>
<td>45.6 ± 12.6</td>
<td>24.5 ± 10.8</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>14.0 ± 11.7</td>
<td>11.2 ± 9.1</td>
<td>0.28*</td>
</tr>
<tr>
<td>Familiar history for atopy</td>
<td>28</td>
<td>36</td>
<td>0.16†</td>
</tr>
<tr>
<td>Personal history for atopy</td>
<td>33</td>
<td>34</td>
<td>0.94†</td>
</tr>
<tr>
<td>Positive skin-prick test</td>
<td>16</td>
<td>29</td>
<td>0.20†</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>28</td>
<td>44</td>
<td>0.001†</td>
</tr>
<tr>
<td>Sensitization to Dermatophagoides</td>
<td>5</td>
<td>20</td>
<td>0.006†</td>
</tr>
<tr>
<td>Perennial course of symptoms</td>
<td>24</td>
<td>36</td>
<td>0.036†</td>
</tr>
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*Mann-Whitney test for unpaired samples.
†X².

It was also expressed as the maximum attainable FEV₁ posttreatment (FEV₁/PT), ie, the maximum FEV₁ value in percent of predicted, attained over the observed period, as an effect of treatment whatsoever (ie, either immediately after salbutamol or within 1 month after therapy, whichever was higher). On the basis of degree of reversibility, all the studied patients were identified as reversible (ΔFEV₁/B% ≥ 15%) or nonreversible (ΔFEV₁/B% < 15%).

Statistical Analysis

The statistical analysis was performed using the Mann-Whitney test for unpaired samples, frequency of distribution (X²), and linear regression analysis. Analysis of covariance was used for testing differences between slopes. A probability level of p ≤ 0.05 was selected as statistically significant.

RESULTS

Data relevant to age and to disease characteristics of the groups are presented in Table 1. The mean age at the onset of symptoms was 45.6 ± 12.6 years in group A and 24.5 ± 10.8 years in group B. The difference was statistically significant (p < 0.0001). Conversely, the difference in mean disease durations was not significant, in keeping with the selection criteria.

The groups did not differ in their atopic characteristics (positivity for familiar and personal history, for skin prick tests to most common allergens, or both); however, the sensitization to Dermatophagoides pteronyssinus was more frequent in the younger group (p < 0.01); accordingly, a perennial course of symptoms was more frequent in the same group (p < 0.04). No difference between groups was found for usual provoking factors, with the exception of nocturnal sleep, which was more frequently reported as associated with recurrence of attacks in the younger group (p = 0.001) (Table 1).

Concerning the functional assessment, mean data for both groups are presented in Table 3. Because of the selection criteria, the mean degree of obstruction under baseline conditions, expressed by FEV₁/B% and the FEV₁/FVC ratio, was not significantly different between groups. The treatment-induced

<table>
<thead>
<tr>
<th>Drug Association</th>
<th>Older Group</th>
<th>Younger Group</th>
</tr>
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<tbody>
<tr>
<td>B₂*</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>IS</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B₂ + IS</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>SS</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

*B₂ = short-acting B₂-agonist, as needed; IS = inhaled steroids; B₂ + IS = inhaled steroids + B₂-agonist, as needed; SS = systemic steroids; N = no therapy. \( \chi^2 \) p value: 0.12
changes in airway obstruction values, expressed by \( \Delta \text{FEV}_1 \%) and recorded after the baseline bronchodilator test, were 7.2 \pm 8.9 in the older group and 13.2 \pm 12.0 in the younger one \((p = 0.0501)\). After the 4-week course of steroids, the mean overall values were 12.0 \pm 17.5 in the older group and 16.0 \pm 23.9 in the other group. This difference was not statistically significant \((p = 0.36)\).

The number of responder patients \((ie, showing a \Delta \text{FEV}_1 \%) \geq 15\%) after the baseline bronchodilator test was 7 of 50 in the older group and 23 of 51 in the younger one \((p < 0.001)\). Among 71 patients who did not respond to this bronchodilator test, 9 of 43 of the older group and 6 of 28 of the younger one became responders, \(ie, they had a \Delta \text{FEV}_1 \%) level of \( \geq 15\% \) after the steroid course; the difference was not statistically significant \((p = 0.14)\). For the patients who remained nonresponders after the steroid course, in no case did the new bronchodilator test result in a response as defined above. If the overall result \((ie, whenever achieved)\) is considered, the number of responders was significantly higher in the younger group \((29, corresponding to 57\%)\) as compared with the older one \((16 or 32\%, p < 0.02)\); however, within the subsets of responders, the magnitude of \( \Delta \text{FEV}_1 \%) was not significantly different between the two groups. The average \( \text{FEV}_1 \%)_\text{PT}, \(ie, the functional level attainable as an effect of treatment, was significantly lower in the older group \((79.8 \pm 14.8\% \) and 90.8 \pm 17.4\% in group B, \(p = 0.0006)\).

Within each group, \( \text{FEV}_1 \%)B\) did not correlate with age \((p > 0.50)\) but it was directly correlated with the age at the first onset of symptoms \((p < 0.01\) in the younger group, \(p < 0.05\) in the older one) and inversely correlated with the duration of the disease \((p < 0.01\) in younger patients, \(p < 0.03\) in the older group) \(Fig. 1)\.

The magnitude of change in airway obstruction \((\Delta \text{FEV}_1 \%)\) was inversely related with the baseline level of \( \text{FEV}_1 \) in both groups with very similar slopes and intercepts \(Fig. 2); however, no correlation was found between \(\Delta \text{FEV}_1 \%) \(as a dependent variable)\) and the dependent variables age, age at the first symptom onset, and duration of disease \((p > 0.15)\).

\( \text{FEV}_1 \%)_\text{PT}\) correlated with the degree of baseline obstruction in both groups, showing very similar slopes \(Fig. 3)\, but was not correlated with age. \( \text{FEV}_1 \%)_\text{PT}\) was also correlated with the duration of the disease in both groups \(Fig. 4)\. It is of interest that the slope of this relationship was nearly doubled in the younger group \((-0.96, p < 0.0001)\) with respect to the older one \((-0.48, p < 0.01)\)—the difference between slopes was statistically significant \(analysis of covariance, p < 0.001)\.

The proportion of patients with early-onset asthma \((38 in the older group vs 37 in the younger one)\ was not statistically different between groups. For the

### Table 3—Functional Data

<table>
<thead>
<tr>
<th></th>
<th>Older Group</th>
<th>Younger Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{FEV}_1 %) \text{B}%</td>
<td>67.8 \pm 20.3</td>
<td>73.0 \pm 19.6</td>
<td>0.19</td>
</tr>
<tr>
<td>( \text{FEV}<em>1 %)</em>\text{PT}%</td>
<td>64.9 \pm 14.0</td>
<td>63.9 \pm 12.2</td>
<td>0.71</td>
</tr>
<tr>
<td>( \Delta \text{FEV}_1 %) %</td>
<td>12.0 \pm 17.5</td>
<td>16.0 \pm 23.9</td>
<td>0.36</td>
</tr>
<tr>
<td>( \text{FEV}<em>1 %)</em>\text{PT}%</td>
<td>79.8 \pm 14.8</td>
<td>90.7 \pm 17.5</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

**Figure 1.** Correlation between baseline \( \text{FEV}_1 \% \) level \((% \text{pred} - \text{FEV}_1 \%) \text{B}\%) and duration of disease in individual patients; groups are identified by different symbols.
Figure 2. Correlation between percentage change in FEV\textsubscript{1} as an effect of treatment (ΔFEV\textsubscript{1}%) and FEV\textsubscript{1} baseline level (FEV\textsubscript{1}B%).

Comparison between the two subsets within each group (Fig. 5), the late- and early-onset subsets did not differ in terms of FEV\textsubscript{1}B% (p > 0.30), whereas the FEV\textsubscript{1}/FVC% ratio was significantly lower in the early-onset subset of the younger group (p < 0.03). In response to treatment, the two subsets within each group did not differ for ΔFEV\textsubscript{1}% (p > 0.13), but FEV\textsubscript{1}%PT was significantly lower in the early-onset patients of the younger group than in the late-onset patients of the same group (p = 0.008). Comparing the two early-onset subsets, the differences in FEV\textsubscript{1}B%, FEV\textsubscript{1}/FVC%, ΔFEV\textsubscript{1}%, and FEV\textsubscript{1}%PT were not statistically significant; the two late-onset subsets differed significantly only for FEV\textsubscript{1}%PT (p = 0.03), the value being higher in younger patients.

DISCUSSION

The present study was designed to detect the effects of aging on the degree of airway obstruction...
and on the responsiveness to treatment in patients with chronic asthma. In this respect, the condition of asthmatic lung in the aged is under the effect of the following time-related confounding variables: first, it is common that patients have been exposed for decades to noxious stimuli, including tobacco smoke and occupational factors. This exposure often prevents a reliable differential diagnosis with respect to COPD. In order to eliminate this obstacle, we included only lifelong non-smokers without any history of professional exposure likely to cause chronic bronchitis. Second, in elderly patients the disease is seldom of recent acquisition, so the influence of its long duration cannot be easily separated from the effect of aging. To account for this factor we compared groups of different age but with similar duration of disease. The groups did not differ for the prevalence of atopy, although sensitization to mites and perennial course of symptoms was less frequent in the older group. Another distinguishing feature of this group is represented by the evidence of nocturnal sleep reported as a provoking factor less frequently than in the younger group. This finding may be interpreted to be related to a lack of awareness of nocturnal deterioration of airway function noticed in the majority of elderly patients and to a blunted perception of mechanical and chemical loads.

Within a comparable range of alterations in the two groups under investigation, our results show that the degree of functional impairment under baseline conditions is not directly influenced by the process of aging per se, as demonstrated by the lack of correlation between FEV$_1$B% and age. Moreover, there is no evidence of interaction between aging and duration of the disease, since the slopes of the correlations between FEV$_1$B% and duration (which are significant) do not differ between the groups of different age. Therefore, at least in adults, the length of exposure to the effects of the disease—indepedent of the age of the patient—appears to be the time variable affecting the baseline airway caliber. Our results are in agreement with a previous longitudinal study on the functional decline over several years in asthma, where no correlation between the slopes of individual FEV$_1$ decay over time and ages was found. However, in another study based on a single spirometric control of patients with asthma 10 years after previous observations, age was associated with a steeper decline in FEV$_1$, whereas the latter was not correlated with duration of disease. It must be noted that in both studies about one third of patients were current or former smokers, and this status limits the applicability of these data, given the well known effects of smoking on the decline of FEV$_1$.

This issue will remain controversial until data on pathologic changes are produced. Despite the increasing interest on airway remodeling, a single un conclusive study addresses the question of the structural effects of a long-standing disease in elderly patients: By examining the lungs of six elderly patients with a very long past history of severe asthma (mean duration, 45 years), Sobonya did not recognize any peculiar qualitative nor quantitative alteration and recorded in some, but not in all, only the usual inflammatory and fibrotic changes of small airways.

A similar paucity of experimental data may be
observed in the effects of aging on the responsiveness to antiasthmatic treatment. Braman et al.\textsuperscript{17} comparing two groups of elderly patients with asthma with different mean duration of illness (32 vs 5 years), reported that patients with early-onset asthma showed a significantly lesser degree of response to the inhalation of a bronchodilator. This finding confirmed \textit{in vivo} some previous reports on an aging-associated decrease in $\beta$-adrenergic receptor sensitivity,\textsuperscript{5} advocated as a possible pathogenetic factor in late-onset asthma.\textsuperscript{3} In a study on the acute effects of treatment on patients with severe exacerbations of asthma, Petheram\textsuperscript{18} showed that the rates of improvement were similar in elderly patients with respect to younger patients with asthma; however, elderly patients with more severe asthma, already being treated with oral corticosteroids, showed more difficulties in recovering the predicted functional values with respect to younger patients.

The purpose of the present study was to evaluate both the immediate bronchodilation response and the effect of anti-inflammatory treatment, by comparing groups of different age. In evaluating the reversibility, the index most widely used is the one that expresses the change in $FEV_1$ as a percentage of the baseline value. A possible drawback of this method is represented by the fact that small absolute changes become large percentage changes in patients with a low $FEV_1$ level. This could influence the interpretation when comparing results coming from groups with different lung size or with different degree of airway caliber (as in the case of young and elderly patients).\textsuperscript{19} Therefore, in our study we expressed the bronchodilation response in percent predicted. On this basis our results show that aging may affect the acute responsivity to a bronchodilator. Concerning the acute bronchodilation on the starting day, both the average degree of change and the number of responders are significantly higher in the younger group. This result is consistent with either a lesser contribution of bronchial smooth muscle to obstruction or a blunted responsiveness of the same muscle, which is in agreement with the previously cited evidence of an age-related decreased sensitivity to $\beta$-adrenergic receptor stimulatory drugs.\textsuperscript{5} Conversely, the overall responsivity to a prolonged anti-inflammatory treatment is much less affected by the aging process, indicating that the characteristics of asthma as an inflammatory disorder are maintained even with advancing age. On the average, no statis-
tically significant difference between groups was shown in the maximum degree of response to overall treatment (including steroids) nor in the number of patients reaching the threshold value. On the other hand, from the analysis of correlations, it appears that this response is affected by the severity of baseline airway obstruction (the “horse racing” effect), if considered in terms of percentage increase in FEV	extsubscript{1}. In terms of an attainable level of patency, such response decreases with the length of the history of disease.

Concerning the latter result, there is evidence of an unexpected possible role of aging; the slope of the negative correlation between FEV	extsubscript{1} %PT and disease duration is markedly less steep (nearly halved) in the older group. Although this phenomenon is the result of a cross-sectional study and must be confirmed in carefully performed longitudinal investigations, it suggests that the rate of evolution toward an irreversible loss of function is made slower in elderly patients with asthma. One may hypothesize on this basis that, given a comparable duration of exposure, older age makes the patient less prone to structural alterations (whatever they are) that may result from the persistence of the disease. The interpretation of this finding may only be a matter of speculation. In this perspective it has been proposed that alterations of extracellular matrix components, leading to thickening of epithelial basement membrane, might result in the disease becoming more persistent. Because previous evidence supports a negative balance between collagen production and degradation in senescent animals, it may be hypothesized that aging per se (ie, unlike the duration of disease) lowers the intensity of the events of extracellular matrix remodeling that characterizes chronic asthma and possibly contributes to the loss of reversibility.

In conclusion, many aspects of the problem of asthma in elderly patients need to be elucidated; however, from even a limited number of studies, it appears that, although older patients may have a more “fixed” obstruction, aging per se is not a limiting factor for the application of an effective antiasthmatic treatment. Therefore, only adaptations are expected on the basis of extensive clinical trials that are urgently needed.

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