Impaired Bronchodilator Response to Albuterol in Healthy Elderly Men and Women*

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Background: Lymphocytes of normal elderly subjects and young asthmatics display dysfunctional β-adrenoceptors. If β-adrenoceptor dysfunction were found in senescent airways, it might help explain the pathogenesis of late-onset asthma.

Methods: The bronchodilatory effects of albuterol after methacholine-provoked bronchoconstriction were compared in 17 healthy young (age 20 to 36 years) and 17 healthy elderly (age 60 to 76 years) volunteer subjects. Albuterol was inhaled via dosimeter (initially 7.8 μg, doubling every 7.5 min) with forced expiratory flow at 50% vital capacity (FEF50) measured prior to each dose. Albuterol sensitivity was expressed as the cumulative logarithm of the area under the FEF50 recovery curve (AUC); a greater AUC meant lower sensitivity. On another study day, spontaneous recovery from methacholine was assessed similarly.

Results: There was no intergroup difference in spontaneous recovery. Despite lower methacholine doses provoking similar (35%) FEF50 falls in elderly subjects, albuterol AUC was greater in elderly subjects (6,552·min·mg) than young subjects (3,922·min·mg; p=0.03). Multiple regression showed that AUC and age were related (p=0.02).

Conclusion: Airway β2-adrenoceptor responsiveness is diminished in old age, suggesting that airway β-adrenoceptor dysfunction may be implicated in late-onset asthma.

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ANOVA=analysis of variance; AUC=area under the FEF50 recovery curve; CI=confidence interval; FEF50=forced expiratory flow at 50% vital capacity; FEVi=forced expiratory volume in 1 s

Key words: aging; airway responsiveness; albuterol; β-adrenergic receptors; bronchoconstriction; methacholine chloride

Asthma has a prevalence of at least 6.5% in the elderly and is often unrecognized.1,2 Most elderly asthmatics have developed asthma in adulthood.1,3 However, the pathogenesis of late-onset asthma is poorly understood. Reduced β-adrenergic receptor responsiveness, long postulated as a cause of asthma,4 is seen in young asthmatics5-10 and in normal elderly subjects.11-15 Studies of the β-adrenergic system in normal elderly have been confined chiefly to receptor binding, affinity, and functional studies on lymphocytes12-15 or to investigations of cardiovascular response.11 Recently, we have demonstrated inverse relationships between nonspecific bronchial responsiveness to methacholine (characteristic of asthma, its degree correlating with asthma severity,16-18) and lymphocyte β-adrenoceptor function in young drug-naive asthmatic subjects19 and in elderly normal subjects and asthmatics.20 We have shown further that the lymphocyte β-adrenoceptor abnormality associated with late-onset asthma in old age is one of impaired affinity for agonist with preservation of receptor density, different only in degree from that in elderly normal subjects,20 and distinct from the impaired β-adrenoceptor density found in juvenile-onset asthma.6-9,18,19 This would suggest that the mechanisms responsible for β-adrenoceptor dysfunction are similar to those underlying age-associated β-adrenoceptor dysfunction, and that late-onset asthma may represent the extreme end of a spectrum of age-associated β-adrenoceptor dysfunction.

If this hypothesis is correct, one would predict impaired airway bronchodilator response to β-adrenoceptor agonists in normal elderly people. Although such abnormalities recently have been demonstrated in long-standing asthma in old age,3 to our knowledge, there are no studies of airway β-adrenergic responsiveness in the normal elderly. Therefore, the purpose

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of the present study was to compare the bronchodilator responses to nebulized albuterol in elderly normal and young normal subjects following standardized degrees of methacholine-provoked bronchoconstriction.

METHODS

Subjects
Seventeen healthy young (age 20 to 36 years) and 17 elderly (age 60 to 76 years) nonasthmatic subjects were recruited from the community. Subjects had normal baseline lung function with no respiratory or atopic history. Exclusion criteria were: the following conditions: cognitive impairment; pregnancy; cardiac disease; thyroid disorder; present cigarette smoking or smoking history of >10 pack-years; respiratory infection; medication change, or antihistamine treatment within 6 weeks; past or present treatment with β-adrenergic antagonists, β-adrenergic agonists, calcium antagonists, or angiotensin-converting enzyme inhibitors; and baseline FEV₁ (each study day) less the 60% of predicted.

Volunteers were screened with a medical history, physical examination, and electrocardiogram. A serum pregnancy test was performed when appropriate. Subjects refrained from coffee and oral medications for 24 h before each study period.

Study Protocol
The present study, which specifically investigated the reversal of bronchoconstriction by a β₂-adrenoceptor agonist, formed part of a larger protocol reported elsewhere that was designed primarily to evaluate the effect of age on bronchial responsiveness to methacholine. Subjects were studied on consecutive days (but within 10 days) according to the following regimen.

Day 1: After voiding urine, subjects rested in a semirecumbent position for 30 min. Pulse rate and blood pressure were measured. An inhaled methacholine challenge was administered by a modified dosimeter (Newcastle) method starting with an initial dose of 1.5 μg methacholine chloride in normal saline solution and continuing with doubling cumulative doses at 5-min intervals. Single measurements of flow-volume loops were obtained immediately before each dose. End points comprised a 35% fall in maximal expiratory flow at 50% of vital capacity (FEF50) or administration of the maximum cumulative dose of 6.4 mg methacholine chloride. Flow-volume loops were measured (Gould 5000 IV Pulmonary Function Unit; Gould; Dayton, Ohio). FEF50 was monitored by single flow-volume loops at 7.5-min intervals until it returned to normal. A bronchodilator was not given. Output of nebulizers (12 Acorn System 22 Turbo nebulizers; Medic-Aid Ltd; Bognor Regis, West Sussex, England) was maintained at 10 μL per nebulization (SD, 0.9 to 2.5%) by computer-controlled variation of nebulization time. Subjects were seated during the flow-volume loop measurements.

Day 2: A methacholine challenge was administered as on day 1. Following the methacholine challenge, nebulized albuterol was administered from the dosimeter in doubling cumulative doses at 7.5-min intervals, beginning with a dose of 7.8 μg. Bronchodilatation was monitored as on day 1 with single flow-volume loops immediately before each albuterol dose. The end point for albuterol administration was a return of FEF50 to 100% or more of its baseline value.

Day 3: The procedures for day 2 were repeated.

All subjects gave written informed consent to participate in the protocol, which was approved by the Human Subjects Committee of the University of Washington and the Research and Development Committee of the Boise VA Medical Center.

Data Analysis and Statistics
The following information was derived for each subject: (1) maximum percentage fall in FEF50 provoked by inhaled methacholine on all 3 days; (2) total dose of methacholine administered; (3) total dose of albuterol needed to return FEF50 to baseline; (4) the area above the “spontaneous recovery curve” (day 1) was calculated by the trapezoidal rule (Fig 1). This represents a measure of the rate of spontaneous recovery from bronchoconstriction following methacholine challenge. Area units for this calculation are percent fall in FEF50 multiplied by time in minutes (%-min). (5) The area above the “albuterol recovery curves” (days 2 and 3) were calculated by a more complex formula. Because simple area fails to take account of the logarithmic progression of albuterol dosage (doubling doses every 7.5 min), a “logarithmic area” was calculated by dividing each total area (determined by the trapezoidal rule) into 7.5-min time units and multiplying each unit area by the total cumulative albuterol dose acting within the time unit (Fig 2). Units are percent fall in FEF50 multiplied by time in minutes and the albuterol dose in micrograms (%-min-μg).

Reproducibility of the total albuterol dose needed for recovery was calculated by the method of Bland and Altman. Two-way analysis of variance (ANOVA) with replication was used to compare the time course of spontaneous recovery with the time course following albuterol within each age group and to compare the time courses with and without albuterol treatment in the two groups. Paired t-tests were used to compare simple areas above the spontaneous recovery curves and albuterol recovery curves within subject groups (ie, to ensure that albuterol was increasing the rate of recovery). One-way ANOVA was employed to examine potential differences in baseline values and in area above the curves between subject groups. For the area above the albuterol recovery curve, prior covariate analysis was employed before ANOVA to allow for clinical investigations.
Table 1—Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>No. (M,F)</th>
<th>Age, yr</th>
<th>Baseline FEV₁, % Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>17 (8M,9F)</td>
<td>29.4±5.4</td>
<td>105.9±10.7</td>
</tr>
<tr>
<td>Elderly</td>
<td>17 (11M,6F)</td>
<td>67.2±5.5</td>
<td>109.1±13.0</td>
</tr>
</tbody>
</table>

*Values are mean±SD.

1Reference values for FEV₁ are based on data of Morris.37

differences in total methacholine dose (log value), baseline lung function, and percentage fall in FEF50. Multiple regression analysis was employed to assess the relationship between area above the albuterol recovery curve and age, taking account of other variables, including sex differences. Unless otherwise stated, results are expressed as mean ± SD. Statistical significance was defined at the 5% level.

**RESULTS**

For simplicity of presentation, data given will refer to day 2 unless otherwise stated. Analyses revealed very similar results on days 2 and 3.

**Subjects Characteristics**

Subject characteristics are shown in Table 1. As previously reported,20 there was no difference in baseline FEV₁ (percent predicted) between groups.

**Methacholine Challenge**

In accord with the aim of the methacholine challenge protocol, there was no difference in the maximum percentage fall in FEF50 between the elderly (36.8±8.6%) and the young (33.3±11.1%) groups (F₁,₂₀=0.83, p=0.4). However the elderly subjects required a much lower total cumulative dose of methacholine (38 µg, 95% confidence interval [CI]=164 to 895 µg) than did the young (5,010 µg, 95% CI=4,086 to 6,145 µg; F₁,₂₀=39.1, p<0.001). Thus, the elderly were more responsive to inhaled methacholine than the young. As previously reported,20 the results of the methacholine challenges were reproducible, with (for all subjects) a coefficient of repeatability22 of 0.414 and 5% confidence limits for repeat determination of the slope of the FEF50 dose-response curve of 0.39×initial slope to 2.59×initial slope.

**Reproducibility of Albuterol Recovery**

Geometric mean total doses of albuterol needed to return FEF50 to its baseline value on days 2 and 3, in all 34 subjects, were 37.6 and 47.3 µg, respectively. The geometric mean of the ratio of the albuterol dose on day 2 to the albuterol dose on day 3 was 0.93 (95% CI=0.73 to 1.13). The coefficient of repeatability22 was 0.539. The 95% CI for repeat estimation of albuterol dose needed for recovery in young and elderly subjects was 0.29 to 3.36 multiplied by the initial dose.

**Area Above Spontaneous Recovery Curve**

The time courses of spontaneous recovery after methacholine in the young subjects (Fig 3) and in the elderly subjects (Fig 4) were not significantly different (F₅,₁₇₄=1.13, p=0.34). The area above the spontaneous recovery curve was 1,330±441%-min for elderly subjects and 1,295±445%-min for young subjects. This difference was not significant (F₁,₂₀=0.11, p=0.7).

**Albuterol Recovery Curve vs Spontaneous Recovery Curve**

The time course of recovery after albuterol was significantly more rapid than the time course of spontaneous recovery in both the young subjects (Fig 3; F₅,₈₄=21.82, p<0.001) and in the elderly subjects (Fig 4; F₅,₈₄=18.03, p<0.001). Also, the time course of recovery after albuterol in the elderly subjects (Fig 4) was slower than in the young subjects (Fig 3). The ANOVA confirmed that this difference was significant (F₅,₈₄=...
**Table 2—Results of Multiple Regression Analysis of Logarithmic Area Above the Albuterol Recovery Curve as a Function of Age and Other Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>SE</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.020</td>
<td>0.008</td>
<td>2.44</td>
<td>0.02</td>
</tr>
<tr>
<td>Log methacholine dose</td>
<td>0.27</td>
<td>0.18</td>
<td>1.49</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline FEV₁</td>
<td>0.16</td>
<td>0.14</td>
<td>1.17</td>
<td>0.25</td>
</tr>
<tr>
<td>% Fall in FEF50</td>
<td>0.017</td>
<td>0.009</td>
<td>1.77</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Overall R²=0.23; b=partial regression coefficient; SE=standard error; t=Student’s t value; R=coefficient of multiple regression. Log methacholine dose is the logarithm of the total methacholine dose administered to each subject.

41.23, p=0.004). For elderly subjects, the simple area above the albuterol recovery curve was 483±299%-min (t=7.8, p<0.001 vs area above spontaneous recovery curve). For young subjects, the simple area above the albuterol recovery curve was 413±202%-min (t=7.9, p<0.001 vs area above the spontaneous recovery curve).

**Area Above Albuterol Recovery Curve**

The logarithmic area above the albuterol recovery curve was greater in the elderly (6,552; 95% CI=3,510 to 12,218) than in the young (3,922; 95% CI=2,295 to 6,690; F₁,2₅=5.05, p=0.033). The ANOVA did not show significant effects of baseline FEV₁, percent fall FEF50, or log dose methacholine on the logarithmic area above the albuterol recovery curve. Multiple regression analysis of logarithmic area above the albuterol recovery curve against age, methacholine dose, baseline lung function, and percent fall in FEF50 (Table 2) revealed a significant relationship only to age (p=0.022). However, the overall coefficient of multiple regression (R) indicates that less than 25% of the variance in albuterol recovery could be explained by these variables. Further regression analysis revealed no relationship between logarithmic area above the albuterol recovery curve and slope of the methacholine dose-response curve.

**DISCUSSION**

The present study has validated a method for the assessment of bronchodilator sensitivity to albuterol in normal subjects without baseline bronchoconstriction. Reproducibility of the results was good and compares well with reproducibility of bronchoconstrictor challenge with methacholine using this protocol in both young and elderly subjects. The study showed an impaired bronchodilator response to a β₂-adrenergic agonist in healthy elderly subjects following methacholine challenge. The elderly required longer after albuterol inhalation to reverse the same degree of methacholine-provoked bronchoconstriction. This was the case despite the fact that they needed less methacholine to produce an equal degree of bronchoconstriction. Since baseline lung function was normal in all subjects and spontaneous reversibility (day 1) was almost identical in young and elderly groups, the observed differences were unlikely to be the result of other intrinsic factors.

Abnormalities of β-adrenergic receptor function are well recognized in young asthmatics and have been suggested as a cause of asthma for many years. Similar abnormalities are seen in normal elderly subjects and may be the result of aging of the β-adrenergic receptor adenyl cyclase system.

Whereas lymphocytes and lung membranes of young asthmatics have reduced numbers (density) of β-adrenoceptors, the healthy elderly subjects have normal lymphocyte membrane receptor density with a reduced receptor affinity for agonist. This is thought to represent functional uncoupling of the receptor from the adenyl cyclase complex, and is associated with impaired receptor-mediated adenyl cyclase activity. Impaired adenyl cyclase activity is common to asthma and normal aging. Studies performed in our laboratory have demonstrated that age-associated changes in in vitro β-adrenergic receptor affinity are greater in elderly patients with late-onset asthma compared with elderly normal subjects. These studies also have confirmed a relationship between such changes and nonspecific bronchial responsiveness (NSBR) to inhaled methacholine. The fact that these changes are distinct from the reductions in receptor density previously reported in those with juvenile-onset asthma and confirmed in our laboratory provides some evidence that late-onset asthma may represent the extreme end of a spectrum of aging effects on the β-adrenoceptor pathway. Demonstration of an extension of age-related receptor dysfunction, previously shown in vitro and in cardiovascular response, to airway response is an essential element of this hypothesis. Before this study, to our knowledge, there has been no examination of age-associated β-adrenoceptor function in the airway.

There is, nevertheless, controversy over the magnitude of the role that β-adrenoceptor dysfunction plays in the pathogenesis of asthma in general. Although short-term intravenous β-blockade potentiates NSBR in young nonasthmatics, the potentiation is small (up to fourfold), whereas elderly asthmatics in a previous study in our laboratory possessed a degree of NSBR 2,000 times that of young normal subjects. The elderly normal subjects in the present study required over 100-fold less methacholine to achieve the same degree of bronchoconstriction as young normal subjects, which means that the elderly were over 100 times more responsive than the young. However, the β-blockade model is likely to represent an oversimplification of the pathophysiology of chronic β-adrenergic receptor dysfunction. Short-term intravenous β-blockade would not produce immediate effects via other β-adrenergic dependent mechanisms such as lung microvascular
leakage, alveolar permeability, surfactant secretion, inhibition of mast cell mediator release and neutrophil lysozyme secretion, and stimulation of ciliated epithelial function.\textsuperscript{30} However, modulation of any of these systems could be expected to result in changes in bronchial responsiveness in the medium or long term. Indeed, late asthmatic responses, which are paralleled by increases in NSBR,\textsuperscript{31} are associated with bronchial edema and the release of prostaglandins, leukotrienes, and other mediators from mast cells and other sources. Furthermore, we have previously demonstrated close association among \(\beta\)-adrenergic receptor dysfunction, lack of inhibition of leukocyte respiratory burst (and thus predisposition to release of inflammatory mediators), and bronchial responsiveness in adults across a wide age range.\textsuperscript{32} Finally, the \(\beta\)-adrenergic system also modulates cholinergic neurotransmission at a prejunctional level with effects on endogenous acetylcholine sensitivity up to 100 times more potent than its effects on response to exogenous cholinergic agents.\textsuperscript{33} Thus, it is possible that the relatively small difference in receptor sensitivity to exogenous \(\beta\)-adrenergic agonist that we have shown in the present study could be associated with a much larger endogenous \(\beta\)-adrenergic receptor deficit, compatible with the 100-fold increase in bronchial responsiveness in the elderly group.

An alternative or additional explanation for the discrepancy between the apparently small \(\beta\)-adrenergic deficit and the large increase in bronchial responsiveness seen in the elderly group in the present study may be the effect of functional antagonism between methacholine and albuterol. Our young subjects needed much greater doses of methacholine to produce bronchoconstriction than did the elderly. It is arguable that there would be a tendency for them to require greater doses of albuterol to produce bronchodilatation, thus tending to mask, rather than enhance, any difference in \(\beta\)-adrenergic sensitivity between the two groups. It also might explain the lack of significant relationship between methacholine responsiveness and albuterol sensitivity in the present study.

There remain, however, other possible explanations for the strikingly large increase in methacholine sensitivity in the elderly group. Normal airway tone is thought to be dependent on a balance between activity of the \(\beta\)-adrenergic, \(\alpha\)-adrenergic, and cholinergic pathways together with that of a poorly characterized nonadrenergic, noncholinergic inhibitory pathway. It is clearly possible that increased cholinergic activity in elderly subjects may be implicated in our findings. In patients with asthma and chronic bronchitis, however, both \(\beta\)-adrenergic and cholinergic antagonist bronchodilator responses decline with age,\textsuperscript{34} and although this may be a consequence of structural changes in the airways related to disease or its duration, studies in normal subjects have not shown a relationship between cholinergic or \(\alpha\)-adrenergic reactivity and age.\textsuperscript{35}

The use of FEF50 as the ventilatory parameter was dictated by the need to obtain measurable bronchoconstriction in nonasthmatics. FEF50 has been shown to be the small airway parameter that changes least with age.\textsuperscript{36} Despite the potential for variability in the measurement, our laboratory has previously obtained highly reproducible results for slope of the dose response curve using this parameter,\textsuperscript{20} and the good reproducibility of the albuterol recovery curves in the present study further testifies to the appropriateness of FEF50 in such studies.

The differences observed between elderly and young normal subjects in the present investigation may have implications not only for the understanding of the pathogenesis of asthma in old age but also for the clinical management of asthma in this age group. Recently, Braman and colleagues\textsuperscript{3} have demonstrated an incomplete bronchodilator response to \(\beta\)-adrenergic agonist in elderly asthmatics. Despite their assertion that such incomplete response was mainly a function of duration of asthma, they showed no statistical difference in bronchodilatory effect between two groups of elderly asthmatics whose mean duration of symptoms was 31 years and 5 years, respectively. In the light of the results in the present study, it remains possible that the incomplete response to \(\beta_2\)-adrenergic agonists in elderly asthmatics is at least partly a function of age-related effects on the \(\beta_2\)-adrenergic receptor rather than the duration of asthma, chronic inflammation, and mucus hypersecretion. If confirmed by additional studies, this suggests that attempts to enhance \(\beta\)-adrenergic receptor responsiveness might provide effective adjunctive therapy in this patient population.

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