Ratio Between Forced Expiratory Flow Between 25% and 75% of Vital Capacity and FVC Is a Determinant of Airway Reactivity and Sensitivity to Methacholine*

Annie Lin Parker, MD, FCCP; Muhanned Abu-Hijleh, MD; and F. Dennis McCool, MD, FCCP

Study objective: The ratio between forced expiratory flow between 25% and 75% of vital capacity (FEF25–75) and FVC is thought to reflect dysanapsis between airway size and lung size. A low FEF25–75/FVC ratio is associated with airway responsiveness to methacholine in middle-aged and older men. The current study was designed to assess this relationship in both male and female subjects over a broader range of ages.

Study design: Data analysis of consecutive subjects who had a ≥ 20% reduction in FEV1 after ≤ 189 cumulative units of methacholine over a 7-year period.

Setting: Pulmonary function laboratory in a university-affiliated hospital.

Patients: A total of 764 consecutive subjects aged 4 to 91 years (mean ± SD age, 40.8 ± 19.6 years). There were 223 male (29.3%) and 540 female (70.7%) subjects.

Measurements and results: Airway reactivity was assessed as the dose-response slope of the reduction in FEV₁ from baseline vs the cumulative dose of inhaled methacholine. The cumulative dose of methacholine causing 20% reduction in FEV₁ (PD20) was used as the indicator of airway sensitivity. In a linear regression model that included age, height, and percentage of predicted FEV₁, the FEF25–75/FVC ratio accounted for 7.6% of variability in airway reactivity (p < 0.0001, r² = 0.076). Subjects with higher airway sensitivity, indicated by lower PD20, also had a lower FEF25–75/FVC ratio.

Conclusions: A low FEF25–75/FVC ratio, indicating small airway size relative to lung size, is associated with higher airway sensitivity and reactivity to methacholine in susceptible subjects.

Key words: airway reactivity; airway sensitivity; dysanapsis; methacholine

Abbreviations: cu = cumulative units; DRS = dose-response slope; FEF25–75 = forced expiratory flow between 25% and 75% of vital capacity; PD20 = cumulative dose of methacholine causing 20% reduction in FEV₁; PFT = pulmonary function test; Pst[L50] = static recoil pressure of the lung at 50% of vital capacity; VC = vital capacity; Vmax50 = maximal flow at 50% of vital capacity.

The presence of airway hyperresponsiveness to variable stimuli is considered one of the characteristics of asthma.¹ Airway size is one factor that may determine the presence of airway hyperrespon-

*From the Department of Pulmonary and Critical Care Medicine, Memorial Hospital of Rhode Island and Brown Medical School, Providence, RI.

Manuscript received November 28, 2001; revision accepted January 6, 2003.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Annie Lin Parker, MD, FCCP, Department of Pulmonary and Critical Care Medicine, Memorial Hospital of Rhode Island, 111 Brewster St, Pawtucket, RI 02860; e-mail: Annie_Parker@brown.edu

www.chestjournal.org CHEST / 124 / 1 / JULY, 2003 63
may be more likely to acquire expiratory flow limitation than individuals with higher ratios. In a study of subjects 7 to 29 years of age, a low ratio was found to be a significant predictor of airway hyperresponsiveness to eucapnic hyperventilation of cold air. More recently, in a study of 929 middle-aged and older men, Litonjua et al found a negative association between this ratio and the degree of methacholine airway responsiveness. An epidemiologic study from Europe has also suggested that the size of airway may play an important role in the incidence of asthma.

The current study was designed to assess the relationship of FEF25/75/FVC ratio and methacholine airway responsiveness over a broader range of ages and in a group that included women and children. The airway responsiveness to methacholine was characterized by the following: (1) reactivity, as assessed by the slopes of the methacholine dose-response curve; and (2) sensitivity, expressed by the cumulative dose of methacholine required to cause 20% reduction in FEV1 (PD20).9

**Materials and Methods**

**Study Design**

Consecutive subjects who had a ≥ 20% reduction in FEV1 after ≤ 189 cumulative units (cu) of methacholine between January 1993 and September 2000 were included in the study. Only subjects with known interstitial lung diseases, neuromuscular diseases, and diaphragm paralysis were excluded. All studies were performed in the Pulmonary Function Laboratory of Memorial Hospital of Rhode Island.

**Pulmonary Function Testing**

Spirometry was performed using standard techniques on the spirometer (Transfer Test Model C Apparatus; Morgan Scientific; Haverhill, MA). At least three spirograms were performed until the American Thoracic Society standard for acceptability of the final dose of methacholine inhalation divided by the cumulative dose inhaled. The DRS was expressed in units of the percentage reduction in FEV1 per micromole methacholine. Because of their highly skewed distribution, DRS was logarithmically transformed (log10) for all analysis. A small constant (0.3) was added to each value of DRS to eliminate zero and slightly negative variables. A simple linear regression model was constructed for FEF25/75/FVC ratio and airway reactivity (log10DRS) with log10DRS as the dependent variable.

In another analysis, a multiple linear regression model with log10DRS as the dependent variable was created to include age, height, and FEV1 percentage predicted and a coefficient of determination (r2) was obtained. The FEF25/75/FVC ratio was then added to this model, and a new r2 was obtained. The difference in these two coefficients (r2) was considered the explaining power of the FEF25/75/FVC ratio for the variability in methacholine airway reactivity, independent of age, height, and FEV1. The analyses were then repeated for both genders and four different age groups (≤ 25, > 25 to ≤ 45, > 45 to ≤ 65, and > 65 years).

Airway sensitivity was assessed by the PD20. Subjects were classified into four groups based on PD20: ≤ 1.4 cu, > 1.4 to ≤ 14 cu, > 14 to ≤ 64 cu, and > 64 to ≤ 189 cu. The cumulative unit cut-off for each group corresponded to the increments of methacholine concentration used in our protocol. Differences in FEF25/75/FVC ratio among groups were determined by using analysis of variance and the Fisher least-significant difference multiple-comparison test. Differences were considered significant for p < 0.05. All analyses were performed using Statview (SAS Institute; Cary, NC).

**Results**

A total of 764 subjects were included in this analysis. Sixty-one of the subjects performed only spirometry, and the remaining 703 subjects had both spirometry and lung volume data. The ages of the subjects ranged from 4 to 91 years (mean ± SD, 40.8 ± 19.6 years). There were 224 male (29%) and 540 female (71%) patients. Baseline PFT results of the group were all within normal limits (Table 1). There was a significant association between...
FEF25–75/FVC ratio and airway reactivity as assessed by a simple linear regression with log10DRS as the dependent variable (p < 0.0001, coefficient of determination $r^2 = 0.058$). When a multiple linear regression model with log10DRS as the dependent variable was created to include age, height, and FEV1 percentage of predicted, the $r^2$ was 0.073 (p < 0.0001). The $r^2$ went from 0.073 to 0.149 with an increase of 0.076 when FEF25–75/FVC ratio was added to this model; therefore, the FEF25–75/FVC ratio explained 7.6% of the variability in methacholine airway reactivity, independent of age, height, and FEV1. The analysis was repeated after removing subjects with spirometry data suggestive of overt baseline airway obstruction (FEV1/FVC < 70%). The association between FEF25–75/FVC ratio and log10DRS remained highly significant in the 679 subjects who had an FEV1/FVC ≥ 0.70 (Table 2).

When the group was divided according to gender, male subjects had a lower FEF25–75/FVC ratio compared to female subjects (0.70 ± 0.25 vs 0.80 ± 0.27). The association between FEF25–75/FVC ratio and log10DRS was significant in both male and female subjects (Table 2). The $r^2$ was higher in male subjects (0.146 vs 0.049), but this was most likely due to the smaller sample size (224 male vs 540 female subjects).

The subject groups were then divided into four age groups, and the FEF25–75/FVC ratios were lower in the older age groups (0.94 ± 0.27 for age ≤ 25 years, 0.80 ± 0.23 for age > 25 to ≤ 45 years, 0.68 ± 0.24 for age > 45 and to ≤ 65 years, and 0.55 ± 0.23 for age > 65 years). Male subjects consistently had a lower FEF25–75/FVC ratio than female subjects in every age group. The association between FEF25–75/FVC ratio and airway reactivity remained significant in all age groups, with $r^2$ ranging from 0.052 to 0.136 (Table 3).

Because the smoking status of the subjects was not available, the analysis was not done for smokers vs nonsmokers.

When the analysis was repeated for FEV1 percentage of predicted and log10DRS with log10DRS as the dependent variable, significant association was again noted but with a lower $r^2$ (0.038; p < 0.0001). There was a moderate correlation between FEF25–75/FVC ratio and FEV1 percentage of predicted ($r = 0.47$, p < 0.0001). As expected, there was a much stronger correlation between FEF25–75 and FEF25–75/FVC ratio ($r = 0.54$). Both had significant association with log10DRS in simple linear regression models ($r^2 = 0.10$ for FEF25–75): however, when a multiple regression model was constructed to include age, height, FEV1, FEF25–75, and FEF25–75/FVC ratio with log10DRS as the dependent variable, only FEF25–75/FVC ratio had significant p value (p = 0.02), but not FEV1 (p = 0.21) or FEF25–75 (p = 0.61).

When subjects were grouped according to their airway sensitivity as measured by PD20, there were significant differences in FEF25–75/FVC ratios among the groups (Table 4). Subjects with lower PD20 values, indicating higher airway sensitivity to methacholine, had lower FEF25–75/FVC ratios. When subjects were classified into four quartiles according to their FEF25–75/FVC ratios with similar numbers of patients in each quartile, subjects in the quartile with the lowest FEF25–75/FVC ratio had significantly lower PD20 values compared to subjects in the other three quartiles (all p ≤ 0.0001) [Fig 1]. There was a significant correlation between airway reactivity and sensitivity to methacholine when analysis was made of log10DRS and PD20 ($r = 0.79$, p < 0.0001).
the FEF25 predispose an individual to asthma. Our findings that provide a better understanding of mechanisms that are associated with airway hyperresponsiveness may identify pulmonary function characteristics that may play a role in the pathogenesis of asthma.1 Even though it can be demonstrated in asymptomatic, nonasthmatic subjects, there is evidence that airway hyperresponsiveness has been explored.7,21 Airway hyperresponsiveness may precede the symptoms and clinical diagnosis of asthma in both children and adults.15–17 These findings suggest that airway hyperresponsiveness may play a role in the pathogenesis of asthma. Identifying pulmonary function characteristics that are associated with airway hyperresponsiveness may provide a better understanding of mechanisms that predispose an individual to asthma. Our findings that the FEF25/FVC ratio was significantly associated with airway reactivity and sensitivity suggest that small airways relative to lung size may be a feature that promotes asthma.

### Table 3—Relationship of FEF25–75/FVC Ratio to Airway Reactivity (Log10DRS) by Age and Gender Groups*

<table>
<thead>
<tr>
<th>Age Groups, yr</th>
<th>Patients, No.</th>
<th>Age, yr</th>
<th>Height, inches</th>
<th>FEV1, % predicted</th>
<th>FEF25–75/FVC</th>
<th>r²†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 25</td>
<td>157</td>
<td>16.4 ± 5.5</td>
<td>62.0 ± 6.3</td>
<td>101.4 ± 12.4</td>
<td>0.94 ± 0.27</td>
<td>0.052</td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
<td>15.4 ± 5.7</td>
<td>63.4 ± 5.1</td>
<td>99.1 ± 12.5</td>
<td>0.86 ± 0.25</td>
<td>0.049</td>
</tr>
<tr>
<td>Female</td>
<td>96</td>
<td>16.9 ± 5.4</td>
<td>61.4 ± 5.1</td>
<td>102.5 ± 12.3</td>
<td>0.98 ± 0.24</td>
<td>0.043</td>
</tr>
<tr>
<td>&gt; 25 to ≤ 45</td>
<td>289</td>
<td>35.9 ± 5.5</td>
<td>65.1 ± 3.7</td>
<td>94.1 ± 13.0</td>
<td>0.80 ± 0.23</td>
<td>0.083</td>
</tr>
<tr>
<td>Male</td>
<td>92</td>
<td>35.9 ± 5.5</td>
<td>69.0 ± 2.8</td>
<td>94.0 ± 12.4</td>
<td>0.72 ± 0.18</td>
<td>0.245</td>
</tr>
<tr>
<td>Female</td>
<td>197</td>
<td>35.9 ± 6.1</td>
<td>63.3 ± 2.6</td>
<td>94.2 ± 13.4</td>
<td>0.84 ± 0.24</td>
<td>0.044</td>
</tr>
<tr>
<td>&gt; 45 to ≤ 65</td>
<td>182</td>
<td>54.5 ± 5.7</td>
<td>63.6 ± 3.7</td>
<td>89.0 ± 14.4</td>
<td>0.68 ± 0.24</td>
<td>0.064</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>53.1 ± 6.1</td>
<td>68.3 ± 3.4</td>
<td>83.4 ± 14.4</td>
<td>0.60 ± 0.22</td>
<td>0.195</td>
</tr>
<tr>
<td>Female</td>
<td>139</td>
<td>55.0 ± 5.6</td>
<td>62.2 ± 2.3</td>
<td>90.7 ± 14.0</td>
<td>0.70 ± 0.24</td>
<td>0.038</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>106</td>
<td>73.9 ± 5.8</td>
<td>62.4 ± 3.1</td>
<td>88.3 ± 19.6</td>
<td>0.55 ± 0.23</td>
<td>0.136</td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>74.8 ± 6.3</td>
<td>65.8 ± 2.4</td>
<td>75.8 ± 13.0</td>
<td>0.43 ± 0.20</td>
<td>0.132</td>
</tr>
<tr>
<td>Female</td>
<td>78</td>
<td>73.6 ± 5.6</td>
<td>61.1 ± 2.3</td>
<td>92.8 ± 19.1</td>
<td>0.59 ± 0.22</td>
<td>0.147</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†The difference in r² when the FEF25–75/FVC ratio was added to the baseline linear regression models including age, height, and FEV1 percentage of predicted in the analysis. All p < 0.05 except for male subjects ≤ 25 yr old (p = 0.055).

### Discussion

Analysis of this group of 764 subjects showed significant association between FEF25–75/FVC ratio and airway reactivity and sensitivity. Subjects with lower FEF25–75/FVC ratios had higher airway reactivity and sensitivity to methacholine as assessed by the DRS and PD20. This association existed for both male and female subjects, subjects of various age groups and remained significant after excluding subjects with evidence of overt airway obstruction.

Airway hyperresponsiveness is considered one of the characteristics of asthma.1 Even though it can be demonstrated in asymptomatic, nonasthmatic subjects, there is evidence that airway hyperresponsiveness may precede the symptoms and clinical diagnosis of asthma in both children and adults.15–17 These findings suggest that airway hyperresponsiveness may play a role in the pathogenesis of asthma. Identifying pulmonary function characteristics that are associated with airway hyperresponsiveness may provide a better understanding of mechanisms that predispose an individual to asthma. Our findings that the FEF25–75/FVC ratio was significantly associated with airway reactivity and sensitivity suggest that small airways relative to lung size may be a feature that promotes asthma.

### Table 4—Relationship of FEF25–75/FVC to Airway Sensitivity (PD20)‡

<table>
<thead>
<tr>
<th>PD20, cu</th>
<th>Patients, No.</th>
<th>Age, yr</th>
<th>Height, inches</th>
<th>FEF25–75/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.4</td>
<td>52</td>
<td>43.5 ± 19.6</td>
<td>63.5 ± 4.5</td>
<td>0.61 ± 0.24</td>
</tr>
<tr>
<td>&gt; 1.4 to ≤ 14</td>
<td>226</td>
<td>38.9 ± 20.7</td>
<td>63.0 ± 5.0</td>
<td>0.71 ± 0.29</td>
</tr>
<tr>
<td>&gt; 14 to ≤ 64</td>
<td>233</td>
<td>40.7 ± 19.0</td>
<td>63.7 ± 4.6</td>
<td>0.79 ± 0.24</td>
</tr>
<tr>
<td>&gt; 64 to ≤ 189</td>
<td>253</td>
<td>42.1 ± 19.1</td>
<td>64.2 ± 4.1</td>
<td>0.84 ± 0.26</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
‡All p < 0.05.

Airway responsiveness to methacholine is often analyzed in the construct of airway sensitivity and reactivity. Airway sensitivity can be quantified by the threshold dose of methacholine that leads to a predetermined level of airway narrowing. Factors that can affect airway sensitivity may include intrinsic properties of the airway smooth muscle, the sympathetic and parasympathetic tones, and the level of airway inflammation. Once airway narrowing has been triggered, further airway narrowing may occur in response to a higher dose of methacholine. Airway reactivity represents the degree of further narrowing and can be quantified as the slope of the relationship between the cumulative dose of methacholine and the decrement of FEV1. Airway reactivity may depend on factors such as synthesis of prostaglandins and stimulation of airway irritant receptors and may be independent of factors that affect airway sensitivity. For example, β-adrenergic blockade changes the threshold, but not the slope of the dose-response curves to acetycholine.20

The association between airway size and hyperresponsiveness has been explored.7,21–22 Britton and colleagues1 measured airway reactivity to methacholine in a large, random population sample of adults between the ages of 18 years and 70 years. They demonstrated that at any given age, airway caliber as indicated by the baseline FEV1 in absolute terms or as percentage of predicted, and atopy were the major determinants of airway hyperreactivity in the general population. Kanner et al found a similar association between FEV1 and airway hyperresponsiveness to methacholine in a group of smokers between ages of 35 years and 60 years with mild COPD. The positive association between FEV1 percentage of predicted and log10DRS in our study is consistent with these findings.

We chose to further analyze the association be-
Between airway size and reactivity by considering airway size relative to lung size. Green and colleagues proposed that there were substantial between-individual differences in airway size independent of lung parenchymal size. These differences may have an embryologic basis reflecting physiologically normal but disproportionate growth of the airways and parenchyma within the lung. They termed this phenomenon dysanapsis and speculated that differences in the airway-parenchymal relationship might influence the pathogenesis of airway diseases. Mead subsequently showed that dysanapsis manifested itself by an inverse relationship between vital capacity (VC) and the product of the ratio of maximal flow at 50% of VC (V\textsuperscript{\dot}{max}\textsubscript{50} divided by VC and the static recoil pressure of the lung at 50% of VC (Pst\textsubscript{L}50) \[ V\textsuperscript{\dot}{max}\textsubscript{50}/VC \times Pst\textsubscript{L}50]. A low (V\textsuperscript{\dot}{max}\textsubscript{50}/VC \times Pst\textsubscript{L}50)/VC ratio would indicate smaller airways relative to the lung parenchyma. A less invasive measure of dysanapsis is the FEF\textsubscript{25–75}/FVC ratio. A major advantage of using the FEF\textsubscript{25–75}/FVC ratio is that both parameters can be derived from a maximal expiratory flow-volume loop.

The relationship between the FEF\textsubscript{25–75}/FVC ratio and airway reactivity has been investigated. Litonjua et al found that the FEF\textsubscript{25–75}/FVC ratio was negatively associated with the degree of methacholine airway responsiveness (as assessed by the slope of the log\textsubscript{10} dose and FEV\textsubscript{1} relationship) in a group of 929 middle-aged and older men (average age, 60.5 \pm 7.7 years; range, 41 to 86 years). In their study, FEF\textsubscript{25–75}/FVC ratio explained approximately 5.1% of the variability of log\textsubscript{10}DRS. They concluded that individuals with small airways relative to lung size may be more likely to have hyperresponsive airways than those without dysanapsis.

We extended the findings of Litonjua et al to a group of subjects that included female subjects and younger adults. We confirmed their findings that the FEF\textsubscript{25–75}/FVC ratio is a determinant of airway reactivity to methacholine. In both studies, despite the difference in subject population, the coefficients of determination were in the similar range (5.1% vs 7.6%). We also found that the FEF\textsubscript{25–75}/FVC ratio is a stronger determinant of airway reactivity than FEV\textsubscript{1}. The \( r^2 \) value for FEF\textsubscript{25–75}/FVC ratio was greater than the \( r^2 \) for FEV\textsubscript{1} in simple regression models (0.058 vs 0.038). Given the expected strong correlation between FEF\textsubscript{25–75} and FEF\textsubscript{25–75}/FVC ratio, one may expect the same result for FEF\textsubscript{25–75}. Indeed, a significant association was also noted between FEF\textsubscript{25–75} and airway reactivity. However, in a multiple linear regression model that included age, height, FEV\textsubscript{1}, FEF\textsubscript{25–75}, and FEF\textsubscript{25–75}/FVC ratio with log\textsubscript{10}DRS as the dependent variable, only FEF\textsubscript{25–75}/FVC ratio had a significant p value. These findings suggest that the airway size relative to lung size is a more important determinant of airway reactivity than the absolute size of the airway.

Another characteristic of the airway response to various triggers is airway sensitivity. We assessed

![Figure 1. Relationship of FEF\textsubscript{25–75}/FVC ratio to airway sensitivity (PD\textsubscript{20}). All subjects were classified into four groups according to their FEF\textsubscript{25–75}/FVC ratio with equal number of subjects in each group (quartiles). The mean PD\textsubscript{20} measurements for each quartile were 30.7 cu, 50.5 cu, 58.7 cu, and 54.7 cu. Subjects who had an FEF\textsubscript{25–75}/FVC ratio in the lowest quartile had significantly lower PD\textsubscript{20} compared to subjects in the other three quartiles (all p \leq 0.0001).](image-url)
airway sensitivity as the PD$_{20}$. When subjects were classified into four groups according to their PD$_{20}$, those with lower PD$_{20}$ had lower FEF$25-75$/FVC ratio. Similarly, when subjects were classified into four groups according to their FEF$25-75$/FVC ratio, subjects with the lowest ratio also had the lowest PD$_{20}$. Both findings support the notion that subjects who were more sensitive to methacholine have smaller airway size relative to their lung size.

Dysanapsis between airway size and lung size may have an embryologic basis, but acquired factors such as smoking or inflammation that affect the airway wall thickness may alter the relationship between airway and lung size and lower the FEF$25-75$/FVC ratio. We did not control for the history of smoking or the level of airway inflammation because these data were not available; however, Litonjua and colleagues have found that the association between FEF$25-75$/FVC ratio and methacholine airway responsiveness was not affected by the pack-years of smoking, eosinophil counts, or IgE measurements. These findings suggest that dysanapsis in the form of small airway size relative to lung size, either intrinsic or acquired, will lead to higher airway reactivity and sensitivity to methacholine.

Epidemiologic data on asthma prevalence have demonstrated a gender difference that varies with age. Asthma and wheezing are more prevalent in boys than in girls. During puberty, there is a gender reversal in the prevalence; after puberty, women have a higher prevalence and morbidity rate of asthma than men.

Gender differences in the rate of lung growth and in airway size have been suggested as one of the potential explanations for this phenomenon. Female infants have proportionately larger airways relative to their lung size than do male infants. During childhood and adolescence, the growth of airway, relative to lung parenchyma, occurs faster in teenage boys than in teenage girls. These findings suggest that smaller airways may have a role in the higher prevalence of asthma and wheezing in prepubertal boys; the subsequent faster growth of airways in adolescent male compared to female subjects may partly explain the gender reversal of asthma prevalence after puberty. Male subjects in our study had a lower FEF$25-75$/FVC ratio than female subjects in all age groups. Our subjects were a preselected group who were symptomatic with airway hyperresponsiveness; therefore, the results of persistently lower FEF$25-75$/FVC ratio in male subjects cannot be generalized to a general population. However, the fact that the association of lower FEF$25-75$/FVC ratios with higher airway reactivity and sensitivity exist in both genders and in all age groups suggests that the association between dysanapsis and airway hyperreactivity may be the potential link between anatomic variations and the clinical development of asthma.

We conclude that FEF$25-75$/FVC ratio is a determinant of airway responsiveness to methacholine. A low FEF$25-75$/FVC ratio, indicating small airway size relative to lung size, is associated with higher airway sensitivity and reactivity to methacholine in susceptible subjects.

ACKNOWLEDGMENT: The authors thank Gall Dusseault and Laureen Sheehan for technical support.

REFERENCES

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225–244