Reversibility of Airway Obstruction in Relation to Prognosis in Chronic Obstructive Pulmonary Disease*

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Whether reversibility in airway obstruction with β-adrenergic stimulant is a significant determinant for the outcome was tested in 59 patients with pulmonary emphysema and chronic bronchitis. During four years of follow-up, 43 (73 percent) patients survived and 16 (27 percent) died. Initial VC, FVC, FEV₁, and PaO₂ were significantly smaller, and PaCO₂ was significantly larger in nonsurvivors than those in survivors. After orciprenaline sulfate (10 mg in 0.5 ml solution) inhalation, VC and FEV₁ increased in comparable amount between the two groups. Airway reversibility as estimated by percentage changes in FEV₁ before and after the bronchodilator (reversibility index) was similar between the two groups. In the 16 nonsurvivors, hypoxemic patients had similar FEV₁, FEV₁/FVC, and reversibility indices as normoxemic patients. These results indicate that not airway reversibility per se but a fixed or irreversible component of airway obstruction is one of the determinants of the prognosis in pulmonary emphysema and chronic bronchitis. Chronic hypoxemia is related to neither airway obstruction nor its reversibility, while it does influence the prognosis.

Many physiologic and clinical factors determine the prognosis in patients with chronic obstructive pulmonary disease (COPD). Among these, hypoxemia and cor pulmonale seem to be of critical importance. Spirometric variables such as VC and FEV₁ are also useful to predict the outcome.

Bronchoconstriction is one of the major features of bronchial asthma as well as two other categories of COPD, ie, pulmonary emphysema and chronic bronchitis. However, it is not wholly known whether bronchoconstriction or its reversibility is important in modifying the course and prognosis. It is possible that airflow limitation caused by chronic bronchoconstriction is one of the critical factors leading to hypoxemia due to ventilation-perfusion mismatch and cor pulmonale in these patients.

This report has aimed to evaluate the relation between airway response to inhaled β-adrenergic bronchodilator and prognosis in COPD excluding extrinsic asthma. We believe that the critical analysis of the effect of β-adrenergic stimulants is important from the prognostic point of view because bronchodilators are widely used in clinical practice.

METHODS

The subjects were 59 patients with pulmonary emphysema and chronic bronchitis selected from our background COPD patients (n = 232). They fulfilled the exclusion criteria of extrinsic asthma (below). The diagnosis of pulmonary emphysema and chronic bronchitis was made by detailed medical history, complete physical examination, posteroanterior and lateral chest roentgenograms, bronchoulavolography and alveolography (40 patients), and pulmonary function tests (all patients). Minimal criterion for airway obstruction was FEV₁/FVC below 70 percent after β-adrenergic bronchodilator inhalation. Extrinsic asthematics, diagnosed by reversible attacks of wheezing, eosinophilia, high serum IgE levels, positive skin tests for allergens, a family history of asthma and allergic diseases within second degree relatives, were excluded from the study. Patients whose FEV₁/FVC is below 25 percent, FEV₁ below 20 percent of predicted value, PaO₂ below 45 mm Hg, and PaCO₂ above 70 mm Hg were excluded because they were too disabled to obtain reliable pulmonary function data.

Clinical types of COPD were classified according to the criteria utilizing daily sputum production, Dco/VA and TLC. Briefly, emphysema was assumed to be predominant when daily sputum amount was less than 10 ml, TLC was more than 120 percent of predicted value, and Dco/VA was less than 1.5. These characteristics were assigned as minus values. The opposite characteristics for the three criteria that gave plus value (sputum amount more than 10 ml/24 h, TLC less than 105 percent of predicted value, and Dco/VA more than 3) were used for categorizing bronchitis patients. The patients with zero point were assumed to be intermediate. There were 3I emphysematous, 20 bronchitic, and eight intermediate patients. All patients were in a clinically stable condition (ie, no sign of acute pulmonary inflammation as shown by temperature, chest roentgenograms, erythrocyte sedimentation rate, leukocyte count, C-reactive protein, and gamma-globulin concentration for at least four weeks).

Reversibility of airway obstruction was evaluated by changes in FEV₁ before and ten minutes after the inhalation of orciprenaline sulfate (10 mg in 0.5 ml solution) with an IPPB (Puritan Bennett, type PR-2). Reversibility index was calculated according to the equation:

\[
\text{Reversibility index} = \frac{\text{FEV}_1 \text{after} - \text{FEV}_1 \text{before}}{\text{FEV}_1 \text{before} \times 100}
\]

where, FEV₁, after: FEV₁ after orciprenaline and FEV₁, before: FEV₁ before orciprenaline. Medications, coffee, and tea were restricted at least six hours prior to the study. Routine pulmonary function studies were performed before the inhalation test; spirometry with a bellows type spirometer (VC, FVC, FEV₁, FEV₁/FVC, and MVV), lung
Table 1—Anthropometric and Pulmonary Function Data*

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62±10</td>
<td>61±10</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>158±6</td>
<td>159±5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>50±8</td>
<td>49±6</td>
<td>NS</td>
</tr>
<tr>
<td>VC, L</td>
<td>2.3±0.65</td>
<td>1.92±0.38</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>% VC, %</td>
<td>73±19</td>
<td>59±13</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.05±0.64</td>
<td>1.77±0.33</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.01±0.37</td>
<td>0.79±0.21</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>% FEV1, %</td>
<td>44±18</td>
<td>32±11</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>49±10</td>
<td>45±8</td>
<td>NS</td>
</tr>
<tr>
<td>TLC, L</td>
<td>4.99±1.13</td>
<td>4.94±14</td>
<td>NS</td>
</tr>
<tr>
<td>% TLC, %</td>
<td>116±27</td>
<td>107±30</td>
<td>NS</td>
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<tr>
<td>FRC, L</td>
<td>3.43±0.92</td>
<td>3.7±1.22</td>
<td>NS</td>
</tr>
<tr>
<td>% FRC, %</td>
<td>195±49</td>
<td>201±66</td>
<td>NS</td>
</tr>
<tr>
<td>RV, L</td>
<td>2.52±0.81</td>
<td>2.85±1.22</td>
<td>NS</td>
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<tr>
<td>RV/TLC, %</td>
<td>53±21</td>
<td>35±13</td>
<td>NS</td>
</tr>
<tr>
<td>Dco, ml/min/mm Hg</td>
<td>8.5±5.7</td>
<td>8.4±6.2</td>
<td>NS</td>
</tr>
<tr>
<td>% Dco, %</td>
<td>57±33</td>
<td>48±30</td>
<td>NS</td>
</tr>
<tr>
<td>ΔN2, %/L</td>
<td>11.1±4.1</td>
<td>13.9±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>CV/VC, %</td>
<td>31.7±5.8</td>
<td>35.2±7.6</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.40±0.02</td>
<td>7.38±0.05</td>
<td>NS</td>
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<tr>
<td>PaO2, mm Hg</td>
<td>71±8</td>
<td>62±9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>41±6</td>
<td>46±7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. NS denotes not significant. Percent sign in front of pulmonary function variables denotes percentage of predicted values. Predicted values were obtained from Baldwin et al[1] for VC, Berglund et al[10] for FEV1, Nishida et al[12] for TLC and FRC, and Burrows et al[5] for Dco.

RESULTS

Survival Rates and Pulmonary Function

Of 59 patients, 43 (73 percent) were alive and 16 (27 percent) were dead within four years. The survival rates among emphysematous, bronchitic, and intermedeate patients were not significantly different (77, 65, and 75 percent, respectively).

Comparisons between survivors and nonsurvivors in anthropometric variables are tabulated in Table 1. There were no significant differences in age, height, and weight between the two groups. Mean values for VC, percent VC, FVC, FEV1, and percent FEV1 were significantly smaller in nonsurvivors. No differences were seen in FEV1/FVC. Also there were no differences between the two groups in lung volumes, Dco, CV/VC, and ΔN2. Survivors had significantly higher PaO2 and lower PaCO2 than nonsurvivors, although arterial pH did not differ between the two groups.

Airway Reversibility

After orciprenaline inhalation, VC and FEV1 increased significantly in both survivors and nonsurvivors, while FEV1/FVC did not change (Fig 1). Individual reversibility indices in the two groups are shown in Figure 2. Mean values were 5±SD 11 percent in survivors and 13±11 percent in nonsurvivors (NS).

The occurrence rates of high responders to orciprenaline inhalation (patients with a reversibility index higher than 20 percent) were similar between survivors and nonsurvivors (21 and 25 percent, respectively, NS).

The patients were reclassified into two groups according to the level of PaO2; patients with PaO2 below occurred. A COPD death was considered to be a cause of death only if death was due to respiratory failure or cor pulmonale (confirmed by the medical records).

Comparisons of mean values were examined by Student's t-test and percentage values, by Chi square test. The p values less than 0.05 were assumed to be significant.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21571/ on 06/24/2017)
60 mm Hg (hypoxemic group) and patients with PaO$_2$ above 60 mm Hg (normoxemic group). In the hypoxemic group, nine out of 43 survivors (21 percent) had the reversibility index higher than 20 percent, while four out of 16 nonsurvivors (25 percent) had the index higher than 20 percent, the occurrences being not different ($\chi^2=0.112$, NS). In 16 nonsurvivors, the hypoxemic group (n=9, PaO$_2$=55.9±4.4 mm Hg) had similar FEV$_1$, FEV$_1$/FVC, and reversibility indices as the normoxemic group (n=7, PaO$_2$=70.3±6 mm Hg); FEV$_1$ 0.86±0.24 vs 0.71±0.15, FEV$_1$/FVC 46.6±3.3 vs 43.1±7.4 percent, and a reversibility index of 15±11 vs 9.3±8.9 percent, in hypoxic nonsurvivors vs normoxic nonsurvivors, respectively.

**DISCUSSION**

Once the diagnosis of COPD is made, approximately 40 to 50 percent of patients die within five years because of respiratory failure and/or cor pulmonale.$^{3,5,7}$ These incidences are significantly high compared to those (5 to 10 percent) in the general population of a comparable age.

The course and prognosis of pulmonary emphysema and chronic bronchitis is hardly modified by conventional treatment regimens except by long-term oxygen therapy.$^{6,9}$ An American-Canadian cooperative study showed that IPPB therapy *per se* does not modify outcome, rate, and duration of hospitalizations, change in lung function, and life quality compared to compressor nebulizer therapy.$^{30}$ However, whether bronchodilator therapy is advantageous to improve the life expectancy was not systematically analyzed in this study. In this connection, it may be useful to examine whether or not airway reversibility with bronchodilators is related to the course and prognosis in COPD patients.

Among many prognostic factors, sex, age, clinical types of COPD, nutrition, lung function derangement, frequency of cor pulmonale, history of childhood airway infection, episodes of acute exacerbation, smoking habits, and socioeconomic status are listed to be critical in determining the outcome of COPD patients.$^1$ Previous reports were based on data obtained from patients with chronic airflow limitation including bronchial asthma and “asthmatic” bronchitis. With advances in diagnostic procedures, patients with extrinsic asthma may be differentiated clearly from the other two categories of COPD, *i.e.*, pulmonary emphysema and chronic bronchitis. After excluding extrinsic asthma, our study has demonstrated a similar prognosis between patients with better airway reversibility and those with lesser improvement. However, the relatively small number of patients studied may limit our conclusion.

The death rate of the patients in this study was 27 percent at four years which might be lower than those reported in the other studies of patients with COPD.$^{3,7}$ This may have been caused by the fact that our patient selection was different; one factor may be the exclusion of asthmatics and the other, our bronchial reversibility test not applicable on markedly disabled patients. Probably the latter factor contributed to our lower incidence of COPD death. Nevertheless, our results on routine pulmonary function tests are in good agreement with previous reports.$^{5,3}$ Survivors had significantly higher VC, FVC, and FEV$_1$ both in absolute values and the percentage of predicted values. Higher PaCO$_2$ and lower PaO$_2$ in nonsurvivors are also in accordance with the previous report.$^{11}$

Airway reversibility to inhaled orciprenaline was estimated by the changes in the percentage of FEV$_1$ in our study. A greater than 20 percent improvement in FEV$_1$ was observed in 21 percent of survivors and in 25 percent of nonsurvivors. These patients had neither episodes of asthmatic attacks nor laboratory evidence of extrinsic asthma. They also did not have persons with bronchial asthma and allergic diseases within...
second degree relatives. However, intrinsic asthma may not have been excluded from these patients.

Indicators for the estimation of bronchoconstriction and bronchodilation were used differently among the investigators. If we utilize the absolute values in FEV₁ instead of percentage changes, i.e., differences in FEV₁ before and after bronchodilator,³ there are still no differences between our survivors and nonsurvivors: 0.08 ± 0.11 L in survivors and 0.09 ± 0.09 L in nonsurvivors (NS, Fig 3).

According to the report of Barter and Campbell,¹² smoking may be one of the important determinants in outcome of COPD patients. There were 25 smokers (55 percent) in 43 survivors and six smokers (38 percent) in 16 nonsurvivors (χ² = 0.03, NS). Prevalences of exsmokers were also equivalent between survivors and nonsurvivors (23 and 25 percent, respectively). Thus, smoking habits do not seem to have systematically influenced our results.

Is there any relation between hypoxemia and bronchoconstriction or bronchodilation? Although nonspecific bronchial reactivity was augmented after acute alveolar hypoxia in ewes,¹³ bronchomotor tone and bronchial reactivity did not change directly after hypoxia in asthmatic patients.¹⁴ In fact, our hypoxemic nonsurvivors had similar FEV₁, FEV₁/FVC, and reversibility indexes as normoxemic nonsurvivors, indicating comparable bronchomotor tone between hypoxemic and normoxemic states. Many factors are postulated to influence absorption and clearance rates of aerosolized β-adrenergic stimulant in the bronchial mucous membrane. It is possible that orciprenaline absorption and washout are altered by increased bronchial as well as pulmonary blood flow in the hypoxic state.¹⁵,¹⁶ The diffusion rate of inhaled orciprenaline may be influenced by thickness and surface area of the airways and alveoli that are markedly changed in pulmonary emphysema and chronic bronchitis. In these patients, uneven deposition of inhaled aerosols may be a predominant factor that limits efficient absorption and clearance of β-adrenergic stimulant.

From these considerations, it is interesting that our hypoxemic and normoxemic nonsurvivors had similar levels for bronchomotor tone (as estimated by FEV₁ and FEV₁/FVC) and reversibility index. Airway reactivity to β-adrenergic stimulant has been reported to be one of the critical factors determining prognosis of patients with airflow limitation. However, there is some controversy among the reports. In two prognostic studies, larger airway reversibility was correlated with larger yearly decline in FEV₁.¹⁶,¹⁷ In another report, the percentage increase in FEV₁ after isoproterenol inhalation was documented to be the best discriminator for showing the outcome of patients with COPD.⁸ These facts may designate that FEV₁ after bronchodilator inhalation can be a predictor for the prognosis. In the report of Postma et al,² patients with larger FEV₁ after bronchodilator inhalation had a better prognosis. Based on this, they thought that longterm bronchodilator therapy is beneficial for patients with airflow obstruction. However, “asthmatic” bronchitis was included in their patients, which may modify their results.

Our findings have an important bearing on treatment policy. COPD seems to be an ever progressing disorder whose course and prognosis are little improved by conventional treatment regimens except by long-term oxygen therapy.⁸,⁹ Our failure to find a difference in airway reversibility with inhaled β-adrenergic stimulant between patients with a poor outcome and those with a good prognosis may suggest little beneficial effect of the aerosolized bronchodilator therapy. However, we have focused only on the importance of airway reversibility in late to terminal stages of COPD, thus neglecting changes in airway reversibility.
at earlier stages. This point along with the relatively small number of patients studied may limit our interpretation.

REFERENCES


