Predominant Site of Airway Resistance in Chronic Obstructive Pulmonary Disease*

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The purpose of the present clinical research was to establish the major site of resistance and obstruction in patients with severe, symptomatic chronic obstructive pulmonary disease. We used a noninvasive technique by measuring airflow in a plethysmograph after patients breathed air and after breathing a mixture of 80 percent helium and 20 percent oxygen. In group 1 were 14 patients (mean age, 63 ± 7 years [±1 SD]) with bronchitis. The ratio of their forced expiratory volume in one second over the vital capacity (FEV₁/VC) was 43 ± 10 percent (mean ± 1 SD), and their single-breath carbon monoxide diffusing capacity (Dsb) was normal (125 ± 41 percent of the predicted value). In group 2 were 13 patients with emphysema (mean age, 60 ± 10 years), whose FEV₁/VC was 33 ± 11 percent and Dsb was 55 ± 14 percent of predicted. All patients had abnormally low increases in the maximum expiratory flow at midvital capacity after breathing the helium-oxygen mixture. The range in group 1 was −11 percent to +14 percent and in group 2 was −10 percent to +15 percent. Normal subjects in our laboratory show increases of at least +24 percent. This indicates that the limitation of airflow occurs primarily in the small (<2 mm in internal diameter) and not the large airways.

The site and mechanism of limitation of airflow in chronic bronchitis and emphysema have been controversial. It has generally been assumed that marked increases in total airways resistance (Rₐ) and significant decreases in the forced expiratory volume in one second (FEV₁) are associated with involvement of the large airways. Physiologic studies in normal excised human lungs have demonstrated that the peripheral or small airways, whose internal diameter is less than 2 mm, normally contribute less than 20 percent of total Rₐ. In contrast to normal subjects, studies in excised human lungs from patients who died from severe chronic obstructive pulmonary disease demonstrated that the major increase in Rₐ was in the peripheral or smaller airways. Unfortunately, the techniques to partition Rₐ for these in vitro intrabronchial direct measurements are not suitable for clinical use. The present study attempts to determine the major site of Rₐ in patients with severe chronic obstructive pulmonary disease using a noninvasive technique, ie, measuring airflow after breathing air and a mixture of helium and oxygen. The results of our study indicate that the major site of resistance to airflow in severe chronic obstructive pulmonary disease occurs in the small airways and confirms previous in vitro observations.

MATERIALS AND METHODS

We studied 27 consecutive patients who were seen over a three-month period for severe, symptomatic obstructive pulmonary disease who did not show physiologic improvement with bronchodilator therapy (less than 15 percent improvement). Patients with a history of asthma were excluded. These patients were divided into two categories based upon physiologic pulmonary tests. Studies of pulmonary function were performed with the patient in the sitting position at least six hours following the last bronchodilator medication. Routine spirometric studies were performed using a simple spirometer (Collins). We measured Rₐ and functional residual capacity using a modified volume-displacement whole-body plethysmograph with a volume amplitude frequency response flat to 15 Hz and in phase with mouth flow and esophageal catheter balloon to at least 15 Hz. The mouth pneumotachograph was calibrated for air and for a mixture of 80 percent helium and 20 percent oxygen. Maximal expiratory flow-volume curves were obtained in the plethysmograph and recorded on the X-Y coordinates of a recorder (Hewlett-Packard model 7046A). Initially, maximal expiratory flow-volume curves were obtained while the patient breathed room air and then were repeated after the patient breathed a mixture of 80 percent helium and 20 percent oxygen for a minimum of ten minutes until the level of expired alveolar nitrogen was less than 5 percent. Only those curves with a consistent vital capacity (VC) between tracings agreeing within 5 percent were used in the calculations, and if differences were present (< 5 percent), they were superimposed at total lung capacity (TLC). We measured maximal expiratory flow at 50 percent of the forced vital capacity (Vmax50%) as obtained on air and on the subsequent helium-oxygen.
Table 1—Results of Physiologic Studies

<table>
<thead>
<tr>
<th>Data</th>
<th>Group 1 (Airways)</th>
<th>Group 2 (Emphysema)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>VC, L</td>
<td>2.69 ± 0.80</td>
<td>2.72 ± 0.80</td>
</tr>
<tr>
<td>VC, percent of predicted</td>
<td>75 ± 15</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.16 ± 0.46</td>
<td>0.92 ± 0.40</td>
</tr>
<tr>
<td>FEV₁, percent of predicted</td>
<td>45 ± 16</td>
<td>32 ± 13</td>
</tr>
<tr>
<td>FEV₁/VC, percent</td>
<td>43 ± 10</td>
<td>33 ± 11</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.16 ± 1.20</td>
<td>6.90 ± 1.50</td>
</tr>
<tr>
<td>TLC, percent of predicted</td>
<td>109 ± 17</td>
<td>116 ± 18</td>
</tr>
<tr>
<td>Specific airway conductance,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>percent of predicted</td>
<td>29 ± 19</td>
<td>18 ± 12</td>
</tr>
<tr>
<td>Dsb, percent of predicted</td>
<td>125 ± 41</td>
<td>55 ± 14</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63 ± 7</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>Height, in</td>
<td>66 ± 4</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>(\dot{\text{V}}_{\text{max50%}}, \text{L/sec})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helium-oxygen</td>
<td>2.40 ± 0.75</td>
<td>2.30 ± 0.73</td>
</tr>
<tr>
<td>Air</td>
<td>2.20 ± 0.87</td>
<td>2.10 ± 1.00</td>
</tr>
<tr>
<td>Range of change in</td>
<td>-11 to +14</td>
<td>-10 to +15</td>
</tr>
<tr>
<td>(\text{V}_{\text{max50%}}, \text{percent})**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table values are means ± SD.
**Difference between helium-oxygen mixture and air.

...and 2 appear in Table 1 and Figure 1. All patients were symptomatic and demonstrated severe limitation of airflow. In group 1 were 14 patients with the clinical diagnosis of chronic bronchitis who demonstrated significant obstruction on routine spirometric testing and whose Dsb and elastic recoil pressures were normal. This group represents patients primarily with intrinsic disease of the airways. All of these patients were chronic cigarette smokers. Their mean age was 63 ± 7 years (±1SD), and their mean height was 168 ± 10 cm (66 ± 4 in).

Group 2 included 13 patients who had primarily dyspnea and marked decreases in exercise tolerance and who had minimal complaints of cough, production of sputum, or wheezing (or some combination of the three). These patients all had severe obstruction on routine spirometric testing, and their values for Dsb and elastic recoil pressure were significantly reduced. This group represents patients primarily with emphysema. All were chronic cigarette smokers. Their mean age was 60 + 10 years (± 1 SD) and their mean height was 170 ± 8 cm (67 ± 3 in).

All patients had an abnormal response of \(\dot{\text{V}}_{\text{max50%}}\) while breathing helium and oxygen. The maximum observed increase was 15 percent. The normal minimal increase in \(\dot{\text{V}}_{\text{max50%}}\) after breathing helium and oxygen is greater than 24 percent in our laboratory. Elastic recoil pressure was normal in every patient with normal Dsb, whereas loss of elastic recoil was associated with a reduced Dsb.

**Discussion**

The results of this study demonstrate that in symptomatic patients (excluding asthmatic subjects) with severe obstruction of airflow unresponsive to bronchodilator therapy on routine spirometric testing, the major site of the limitation of airflow...
and increased Raw is in the peripheral or small airways of the lung. Results were similar for patients with predominant bronchitis or emphysema.

We separated patients into the categories of bronchitis and emphysema based on their clinical presentation and Dsb. While nonuniformity of the distribution of ventilation and perfusion may alter the Dsb, low values have previously been reported to correlate well with the morphologic presence of emphysema, whereas normal values were noted only in very mild grades of emphysema. Furthermore, results of pressure-volume curves in all patients categorized as having emphysema based on reduced Dsb demonstrated a loss of elastic recoil.

According to the theory for limitation of airflow proposed by Mead et al., maximal expiratory airflow at a given pulmonary volume is determined by the elastic recoil and the resistance (Rus) between the alveoli and the equal pressure points (EPPs). The EPPs are defined as the point where lateral intrinsic airway pressure is equal to pleural pressure. Downstream to the EPPs, the intraluminal lateral airway pressure is less than pleural pressure, and airways collapse. During most of the maneuver, for forced vital capacity in normal individuals, the EPPs remain predominantly in the large airways, and most of the resistance to airflow is due to the turbulent component of frictional resistance and convective acceleration, both of which are dependent on density. Reduction in gas density, such as occurs after breathing helium and oxygen, will lower the resistance to convective acceleration and the turbulent component of frictional resistance, and flow will improve. In normal subjects or in patients whose major site of resistance is due to obstruction of the large airways, as may occur in asthma, airflow increases after the breathing of helium and oxygen by at least 20 percent at midvital capacity; however, when the major component of resistance is due to the laminar component of frictional resistance, because it is independent of gas density, flow would not be expected to increase with the helium-oxygen mixture. Thus, the response to breathing helium and oxygen is determined by the different components of Raw (Rus).

In the presence of disease or aging, when there is either a loss of elastic recoil (emphysema) or an increase in the intrinsic resistance offered by the peripheral airways (bronchitis) (or both), the EPP will move further upstream toward the alveoli and may be located in peripheral airways, where the total cross-sectional area at EPP is significantly increased. When limitation of airflow occurs in small airways, the laminar component of frictional resistance predominates, which is not dependent on density but on viscosity. Thus, independence from density implies that the EPP has migrated peripherally and the airflow upstream is laminar and fully developed. This upstream displacement of EPP is consistent with our results.

Experimental studies of Barnett demonstrated that the resistance produced by tracheal obstruction was decreased with breathing helium and oxygen, whereas peripheral obstruction induced with histamine was independent of density. Furthermore, the EPP theory appears applicable even in the presence of maldistribution of ventilation. Takashima et al demonstrated in patients with chronic obstruction that during a maximal expiratory flow-volume maneuver the lungs tended to behave as a simple compartment.

Additionally, a reduced Vmax50% with breathing air (as low as 0.8 L/sec) by itself should not preclude the response to the helium-oxygen mixture. In asthmatic subjects, there was no prediction between the helium-oxygen response and the severity of obstruction as measured by Vmax50% with air or by Raw. Despas et al studied six patients with irreversible obstruction of the airways and noted no change in flow rates in five patients after breathing a helium-oxygen mixture. Wellman et al also found abnormal responses to a helium-oxygen mixture in a small group of patients with fixed obstruction of airflow. The investigators suggested that small airways mainly contributed to the limitation of flow. Dosman et al noted abnormal responses to a helium-oxygen mixture in cigarette smokers who otherwise had normal airflow rates. These investigators interpreted this as consistent with early abnormalities of the small airways.

Dosman et al also proposed that an abnormal response to a helium-oxygen mixture is specific for intrinsic disease of the airways and is not affected by loss of elastic recoil. In those patients with bronchitis (group 1) who had a normal diffusing capacity and normal pulmonary elastic recoil, the mechanism of limitation of airflow is predominantly intrinsic disease of the small airways. Our previous studies of mild emphysema would suggest that there may not be significant intrinsic disease of the airways contributing to limitation of airflow; however, in patients with advanced emphysema, as in the present study, anatomic and physiologic studies would also suggest involvement of the small airways in addition to loss of elastic recoil.

**ADDENDUM**

A recent report (Meadows JA III, Rodarte JR, Hyatt RG. Density dependence of maximal expira-
tory flow in chronic obstructive pulmonary disease. Am Rev Respir Dis 1980; 121:47-53) indicated that 11 of 22 patients had normal density dependence of \( V_{\text{max}} \). However, in contrast to the patients in the present report, their patients showed marked improvement in \( V_{\text{max}} \) after bronchodilator administration.

References