ORIGINAL RESEARCH

Lung Hyperinflation and Its Reversibility in Patients with Airway Obstruction of Varying Severity

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ABSTRACT

The natural history of lung hyperinflation in patients with airway obstruction is unknown. In particular, little information exists about the extent of air trapping and its reversibility to bronchodilator therapy in those with mild airway obstruction. We completed a retrospective analysis of data from individuals with airway obstruction who attended our pulmonary function laboratory and had plethysmographic lung volume measurements pre- and post-bronchodilator (salbutamol). COPD was likely the predominant diagnosis but patients with asthma may have been included. We studied 2,265 subjects (61% male), age 65 ± 9 years (mean ± SD) with a post-bronchodilator FEV₁/FVC < 0.70. We examined relationships between indices of airway obstruction and lung hyperinflation, and measured responses to bronchodilation across subgroups stratified by GOLD criteria. In GOLD stage I, vital capacity (VC) and inspiratory capacity (IC) were in the normal range; pre-bronchodilator residual volume (RV), functional residual capacity (FRC) and specific airway resistance were increased to 135%, 119% and 250% of predicted, respectively. For the group as a whole, RV and FRC increased exponentially as FEV₁ decreased, while VC and IC decreased linearly. Regardless of baseline FEV₁, the most consistent improvement following bronchodilation was RV reduction, in terms of magnitude and responder rate. In conclusion, increases (above normal) in airway resistance and plethysmographic lung volumes were found in those with only minor airway obstruction. Indices of lung hyperinflation increased exponentially as airway obstruction worsened. Those with the greatest resting lung hyperinflation showed the largest bronchodilator-induced volume deflation effects. Reduced air trapping was the predominant response to acute bronchodilation across severity subgroups.

INTRODUCTION

Traditionally, the progression of respiratory impairment in susceptible smokers is charted by the accelerating rate of decline in FEV₁ over time (1). This approach, while useful and convenient, gives only limited information about the relentless deterioration of respiratory mechanics that characterizes chronic obstructive pulmonary disease (COPD). Progressive lung hyperinflation is another salient aspect of physiological deterioration that until recently has been neglected and is the main focus of this study. Given the clear association between lung hyperinflation, dyspnea, exercise intolerance (2), and mortality (3, 4), as well as its partial reversibility to treatment, there is considerable interest in evaluating the clinical utility of this physiological “biomarker” in COPD.

One reasonable hypothesis, recently reiterated by Peter Macklem (5), is that the progressive decrements in FEV₁ largely reflect the erosion of vital capacity (VC) as a consequence of increasing residual volume (RV). In other words, FEV₁ decline mirrors the evolution of lung hyperinflation. Earlier small physiological studies have attested to remarkable heterogeneity in the pathophysiology of mild COPD. Thus, there is evidence that significant peripheral airway closure, maldistribution of

Keywords COPD, Bronchodilator response, Lung volumes, Disease severity
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ventilation, disruption of ventilation-perfusion relations and air trapping can exist (in highly variable combinations) in smokers with minimal or no reduction in FEV1 (6–8). We have recently reported that resting lung volumes [RV, functional residual capacity (FRC) and total lung capacity (TLC)] were consistently increased in small groups of patients with significant exertional dyspnea who met criteria for Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I COPD (9, 10). The existence of air trapping in patients with ostensibly mild airway obstruction has potentially important clinical implications that remain to be studied (11).

There is evidence that lung hyperinflation at rest is partially reversible to bronchodilator therapy and that lung deflation may in turn form the basis for improved respiratory symptoms (12–15). Indeed, it can be argued that improvement in FEV1 following bronchodilator treatment mainly reflects recruitment of VC as a result of reduced air trapping (i.e., reduced RV). Thus, it is known that FEV1/FVC ratio remains unaltered (or even decreases) after bronchodilator treatment at least in more advanced COPD (12–14). The pattern of bronchodilator reversibility in patients with milder airway obstruction (i.e., expired flow versus lung volume effects) is less well studied and will be examined in this study.

The main objectives of this study were to: 1) examine relations between increasing airway obstruction and changes in static lung volume components; 2) determine the nature and extent of physiological impairment in patients with milder air flow obstruction; and 3) determine if the pattern of change in airway function (i.e., flow versus volume response) following acute bronchodilator inhalation would differ in mild and severe airway obstruction.

We therefore conducted a retrospective analysis of a cohort of individuals from our pulmonary function laboratory database in whom plethysmographic lung volume measurements before and after a bronchodilator were available. Although our study population was likely comprised predominantly of patients with COPD, we cannot exclude the possibility that some patients with other obstructive airways diseases (i.e., asthma) were included since complete information on smoking history and clinical diagnosis was not available.

**METHODS**

**Subjects and Design**

This observational study involved a retrospective analysis of pulmonary function test records collected between May 1992 and April 2008 at the Kingston General Hospital’s Pulmonary Function Laboratory. Patients selected from this database were referred for comprehensive pulmonary function tests with reversibility testing. Selection criteria included: males and females 40–80 years of age; body mass index 14–55 kg/m2; post-bronchodilator FEV1/FVC < 0.7; availability of post-bronchodilator static lung volumes (by body plethysmography); and the absence of a referral diagnosis of any lung disease other than COPD.

In the case of repeated follow-up testing within a patient, only the first visit meeting eligibility criteria was used in the analysis. For analysis, subjects were stratified by GOLD stage (16). Since risk of harm to patients was minimal and obtaining patient informed consent impracticable, strict safeguards to ensure confidentiality of personal health data were implemented. The Queen’s University and Affiliated Teaching Hospitals Research Ethics Board approved the use of this data and waived the need for patient informed consent.

A group of our previously studied (17, 18), age-matched (40–80 yrs), healthy non-smokers were used as control subjects to test the validity of the pulmonary function predictive equations used in this analysis.

**Procedures**

Pulmonary function testing (spirometry, body plethysmography, single-breath diffusing capacity) was conducted by experienced respiratory therapists/technicians using automated pulmonary function testing equipment (2130 spirometer with 6200 Autobox DL or V6200 Autobox; SensorMedics, Yorba Linda, CA) in keeping with current recommended standards (19–21). Patients were required to withdraw from all short-acting and long-acting bronchodilators for at least 4 and 12 hours, respectively. Reversibility testing (spirometry, body plethysmography) was performed using salbutamol 200 mcg by metered dose inhaler; post-dose measurements were performed 20-min after inhalation. Predicted normal values were those used in the laboratory at the time of testing (22–25); predicted IC was calculated as predicted TLC minus predicted FRC, predicted ERV was calculated as predicted FRC minus predicted RV.

**Statistical analysis**

Values are reported as means ±SD unless otherwise specified. A p-value of < 0.05 was considered significant in all analyses. A chi-square test for homogeneity was used to assess the differences between the proportions of gender within the entire cohort and each GOLD stage. Differences between means across genders were examined using the unpaired t-test. Frequency distributions were analyzed for normality using the one-sample Kolmogorov-Smirnov test. Non-normal distributions were further examined for skewness (symmetry) or kurtosis (peakedness) which were considered significant if the skewness or kurtosis coefficients were > 2. Comparisons across GOLD stages were analyzed using ANOVA; post-hoc testing of significant variables was performed using t-tests with Bonferroni adjustment for multiple comparisons.

Bronchodilator responsiveness. To avoid bias from differences in baseline measurements, changes in FEV1 and various lung volumes were assessed and compared as percentages of predicted normal values (%pr) (26, 27). The occurrence of a positive bronchodilator response was evaluated as frequency statistics and compared using a chi-square test. A positive response cut-off for FEV1 of at least 10%predicted was selected after considering consensus statements and outcomes of previous studies (12, 26, 27).
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls (n = 128)</th>
<th>GOLD I (n = 620)</th>
<th>GOLD II (n = 1,129)</th>
<th>GOLD III/IV (n = 516)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, %male*</td>
<td>50.0</td>
<td>59.4</td>
<td>58.4</td>
<td>68.0</td>
</tr>
<tr>
<td>Age, years</td>
<td>63 ± 10</td>
<td>65 ± 10</td>
<td>65 ± 9</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168 ± 9</td>
<td>166 ± 9</td>
<td>166 ± 9</td>
<td>167 ± 9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4 ± 3.8</td>
<td>27.9 ± 5.3a</td>
<td>28.0 ± 6.1a</td>
<td>26.4 ± 6.2b</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁, L</td>
<td>—</td>
<td>2.33 ± 0.61a</td>
<td>1.63 ± 0.43b</td>
<td>1.00 ± 0.28c</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁, %predicted</td>
<td>—</td>
<td>93 ± 10a</td>
<td>65 ± 8b</td>
<td>39 ± 8c</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁/FVC, %</td>
<td>—</td>
<td>64 ± 5a</td>
<td>58 ± 8b</td>
<td>45 ± 10c</td>
</tr>
<tr>
<td>Pre-bronchodilator pulmonary function:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, %predicted</td>
<td>114 ± 16</td>
<td>91 ± 9a</td>
<td>60 ± 10b</td>
<td>35 ± 8c</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>75 ± 5</td>
<td>64 ± 6a</td>
<td>58 ± 8b</td>
<td>46 ± 10c</td>
</tr>
<tr>
<td>FEF25–75, %predicted</td>
<td>91 ± 32</td>
<td>44 ± 14a</td>
<td>28 ± 10b</td>
<td>15 ± 6c</td>
</tr>
<tr>
<td>FEF50, %predicted</td>
<td>84 ± 36</td>
<td>39 ± 13a</td>
<td>23 ± 10b</td>
<td>11 ± 5c</td>
</tr>
<tr>
<td>TLC, %predicted</td>
<td>103 ± 11</td>
<td>111 ± 13a</td>
<td>107 ± 17b</td>
<td>116 ± 22c</td>
</tr>
<tr>
<td>SVC, %predicted</td>
<td>112 ± 14</td>
<td>100 ± 12a</td>
<td>78 ± 13b</td>
<td>62 ± 13c</td>
</tr>
<tr>
<td>IC, %predicted</td>
<td>105 ± 18</td>
<td>99 ± 18a</td>
<td>77 ± 17b</td>
<td>57 ± 16c</td>
</tr>
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<td>IC/TLC, %</td>
<td>47 ± 8</td>
<td>41 ± 8a</td>
<td>33 ± 8b</td>
<td>24 ± 7c</td>
</tr>
<tr>
<td>FRC, %predicted</td>
<td>102 ± 19</td>
<td>119 ± 24a</td>
<td>132 ± 30b</td>
<td>166 ± 40c</td>
</tr>
<tr>
<td>RV, %predicted</td>
<td>95 ± 19</td>
<td>135 ± 32a</td>
<td>162 ± 43b</td>
<td>218 ± 62c</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>34 ± 7</td>
<td>45 ± 8a</td>
<td>55 ± 9b</td>
<td>67 ± 8c</td>
</tr>
<tr>
<td>ERV, %predicted</td>
<td>123 ± 55</td>
<td>89 ± 47a</td>
<td>70 ± 38b</td>
<td>61 ± 34c</td>
</tr>
<tr>
<td>sRaw, %predicted</td>
<td>148 ± 55</td>
<td>250 ± 122a</td>
<td>383 ± 183b</td>
<td>643 ± 321c</td>
</tr>
<tr>
<td>SVC-FVC difference, L</td>
<td>0.16 ± 0.21</td>
<td>0.14 ± 0.18a</td>
<td>0.18 ± 0.20b</td>
<td>0.25 ± 0.24c</td>
</tr>
<tr>
<td>DLCO, %predicted</td>
<td>106 ± 21</td>
<td>89 ± 23a</td>
<td>77 ± 21b</td>
<td>60 ± 19c</td>
</tr>
<tr>
<td>DLCO/VA, %predicted</td>
<td>113 ± 17</td>
<td>94 ± 25a</td>
<td>96 ± 27b</td>
<td>86 ± 32b</td>
</tr>
<tr>
<td>VA, % predicted TLC</td>
<td>89 ± 11</td>
<td>90 ± 12a</td>
<td>76 ± 13b</td>
<td>64 ± 14c</td>
</tr>
<tr>
<td>TLC-VA difference, L</td>
<td>0.84 ± 0.51</td>
<td>1.15 ± 0.61a</td>
<td>1.79 ± 0.86b</td>
<td>3.10 ± 1.23c</td>
</tr>
</tbody>
</table>

Values are means ± SD unless otherwise specified.
* p < 0.05 difference across GOLD groups by chi-square analysis.
a, b, c, d GOLD group means with different letters are significantly different from each other after Bonferroni adjustment for multiple comparisons (p < 0.05).

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; ERV, expiratory reserve volume; FEF₂₅₋₇₅, forced mid-expiratory flow; FEF₅₀, forced expiratory flow at 50% of forced vital capacity; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; RV, residual volume; sRaw, specific airway resistance; SVC, slow vital capacity; TLC, total lung capacity; VA, alveolar volume.

Figure 1. Pre- and post-bronchodilator static lung volumes are shown for each GOLD stage group compared with an age-matched healthy control group. Residual volume (RV) and functional residual capacity (FRC) increased progressively as GOLD stage worsened. Total lung capacity increased in GOLD stage I in conjunction with a preserved inspiratory capacity (IC), vital capacity (VC) and expiratory reserve volume (ERV). IC and VC then decreased progressively in GOLD stages II and III/IV.
Because no recognized criteria are available, we arbitrarily selected a similar cut-off of at least 10% predicted for IC and other measured lung volumes. A change of this magnitude falls outside the 95% confidence interval for these measurements, as well as outside the coefficient of variation for repeated measurements, in COPD (28, 29). In addition, we have previously estimated that an increase in IC of ∼10% predicted (or ∼0.3 L) results in clinically important improvements in exertional dyspnea intensity (i.e., reductions of at least 0.5 Borg Scale units) and in exercise endurance (i.e., increases of 20% or more) in moderate to severe COPD (14, 28).

Regression models. Post-bronchodilator measurements expressed as %pr were used for regression analyses evaluating the effect of worsening airflow obstruction (FEV₁) on lung volumes, specific airway resistance (sRaw) and diffusing capacity (DLCO). We first evaluated whether the relationship was linear or non-linear using Box-Cox transformation (30). Regardless of linearity/nonlinearity, we used GOLD stage grouping as a categorical variable for FEV₁ and performed a two-way ANOVA (with interaction) using GOLD stage grouping and sex as categorical variables. A significant interaction term (sex∗GOLD) would indicate a difference between men and women in the volume-FEV₁ relationship. All model fitting was examined using residual analysis and regression diagnostics were performed to identify possible outliers and influential observations.

RESULTS

Of the 2,265 subjects included in this analysis, 1,378 (61%) were male and 887 (39%) were female. Pre-bronchodilator DLCO measurements were available in 2,167 of the included subjects. As there were only 74 patients with a post-bronchodilator FEV₁ < 30% predicted and the presence of chronic respiratory failure could not be confirmed, GOLD stages III and IV were combined into one larger (n = 516) severe-to-very severe group for evaluation in this analysis. There was a similar mean age of 65 yrs within each gender group. GOLD stage distribution was relatively similar in men and women, with the majority in each gender meeting stage II criteria (48 and 53%, respectively). Measurements across age- and height-matched GOLD stage subgroups are reported in Table 1. Lung volume components are summarized in Figure 1.

Measurements from our healthy control group (Table 1) indicated good validity of predictive equations for the majority of patients. Figures 2 and 3 show the relationships between lung volumes, diffusing capacity, and specific airway resistance across GOLD stages and in men and women, respectively.

![Figure 2](image_url). Relationships between forced vital capacity (FVC), residual volume (RV), diffusing capacity of the lung (DLCO) and specific airway resistance (sRaw) are shown against FEV₁ (all measurements expressed as % of predicted normal values). FVC changed linearly with FEV₁, RV and sRaw both increased exponentially as FEV₁ decreased, and DLCO decreased as FEV₁ decreased.
of pulmonary function measurements but underestimated our laboratory’s normative values by at least 5% for FEV\textsubscript{1}, VC, IC, ERV, sRaw, D\textsubscript{LCO} and D\textsubscript{LCO}/VA. Comparisons between the GOLD I group and this age-matched control group showed that all pre-bronchodilator pulmonary function measurements expressed as%predicted were significantly different (p < 0.0005) between groups except for VA and the SVC-FVC difference, which were similar.

**Frequency distributions of pulmonary function measurements**

Pre- and post-bronchodilator measurements expressed as%predicted showed normal distributions for: FEV\textsubscript{1}, FVC, IC, SVC and TLC; as well as the IC/TLC, FRC/TLC and RV/TLC ratios. These measurements were also normally distributed within each GOLD stage subgroup. Positive skewness (significantly longer right tail) was shown in FEF\textsubscript{50}, FRC, RV, ERV, sRaw and D\textsubscript{LCO}. However, the skewed distributions for the group as a whole were largely combinations of normally distributed within each GOLD stage subgroup. Positive skewness expressed as%predicted were significantly different (p < 0.0005). RV and FRC increased together (r = 0.90, p < 0.0005).

The D\textsubscript{LCO}-FEV\textsubscript{1} relation was nonlinear (squared) with wide scatter (Figure 2) while the relation between D\textsubscript{LCO} corrected for alveolar volume (VA) and FEV\textsubscript{1} was poor. As FEV\textsubscript{1} worsened, single-breath VA decreased linearly (r = 0.65, p < 0.0005) and the TLC-VA difference increased exponentially.

**Bronchodilator reversibility**

The magnitude of pre- to post-dose change in lung function measurements across GOLD stages is shown in Table 2 (Figure 3a). There was a small but significant (p < 0.0005) increase in post-bronchodilator FEV\textsubscript{1} in all GOLD subgroups; however, this increase was significantly smaller in stage III/IV than either I or II. FEV\textsubscript{1}/FVC changes were not consistent across subgroups with a small increase of 0.4% (p = 0.97), and a decrease of 1.4% (p < 0.0005) in stages I, II and III/IV, respectively.

The magnitude of the FEV\textsubscript{1} response correlated significantly with the FVC response (r = 0.67, p < 0.0005). In all GOLD groups, the RV response was greatest in magnitude; however, the magnitude of reduction in RV became greater as GOLD stage worsened (III/IV > II > I; p < 0.0005). Bronchodilator-induced reductions in RV%pr correlated with increases in FEV\textsubscript{1}%pr (r = −0.39, p < 0.0005) and sRaw%pr (r = 0.48, p < 0.0005); reductions in RV and FRC were strongly related (r = 0.81, p < 0.0005).

**Table 2.** Bronchodilator reversibility: pre- to post-bronchodilator changes

<table>
<thead>
<tr>
<th></th>
<th>GOLD I (n = 620)</th>
<th>GOLD II (n = 1,129)</th>
<th>GOLD III/IV (n = 516)</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆FEV\textsubscript{1}, L</td>
<td>0.15 ± 0.18</td>
<td>0.14 ± 0.16</td>
<td>0.10 ± 0.12</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%</td>
<td>7 ± 3%</td>
<td>11 ± 12%</td>
<td>13 ± 14%</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>5.6 ± 6.8\textsuperscript{a}</td>
<td>5.5 ± 6.0\textsuperscript{a}</td>
<td>3.9 ± 4.1\textsuperscript{b}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆FEV\textsubscript{1}/FVC,%</td>
<td>0.4 ± 3.7</td>
<td>0.0 ± 4.0</td>
<td>−1.4 ± 4.4</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>1 ± 5\textsuperscript{a}</td>
<td>0 ± 6\textsuperscript{a}</td>
<td>−2 ± 6\textsuperscript{b}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆FEF\textsubscript{50}, L/s</td>
<td>0.13 ± 0.32</td>
<td>0.07 ± 0.22</td>
<td>0.03 ± 0.11</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>3 ± 8\textsuperscript{a}</td>
<td>2 ± 6\textsuperscript{b}</td>
<td>1 ± 3\textsuperscript{c}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆TLC, L</td>
<td>−0.06 ± 0.25</td>
<td>−0.12 ± 0.30</td>
<td>−0.15 ± 0.36</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>−1 ± 4\textsuperscript{a}</td>
<td>−2 ± 5\textsuperscript{b}</td>
<td>−2 ± 5\textsuperscript{b}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆SVC, L</td>
<td>0.15 ± 0.21</td>
<td>0.20 ± 0.25</td>
<td>0.27 ± 0.27</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>4 ± 6\textsuperscript{a}</td>
<td>6 ± 7\textsuperscript{b}</td>
<td>7 ± 7\textsuperscript{c}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆IC, L</td>
<td>0.13 ± 0.26</td>
<td>0.16 ± 0.26</td>
<td>0.20 ± 0.26</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>5 ± 10\textsuperscript{a}</td>
<td>6 ± 9\textsuperscript{b}</td>
<td>7 ± 9\textsuperscript{b}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆FRC, L</td>
<td>−0.18 ± 0.29</td>
<td>−0.28 ± 0.34</td>
<td>−0.33 ± 0.43</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>−6 ± 9\textsuperscript{a}</td>
<td>−9 ± 11\textsuperscript{b}</td>
<td>−10 ± 13\textsuperscript{c}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆RV, L</td>
<td>−0.21 ± 0.33</td>
<td>−0.32 ± 0.38</td>
<td>−0.42 ± 0.47</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>−6 ± 10\textsuperscript{a}</td>
<td>−15 ± 18\textsuperscript{b}</td>
<td>−19 ± 22\textsuperscript{b}</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>∆sRaw, mmHg/L/s × L</td>
<td>−3.0 ± 3.6</td>
<td>−4.4 ± 4.9</td>
<td>−5.7 ± 7.0</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>%predicted</td>
<td>−71 ± 85\textsuperscript{a}</td>
<td>−105 ± 115\textsuperscript{b}</td>
<td>−137 ± 185\textsuperscript{a}</td>
<td>&lt; 0.0005</td>
</tr>
</tbody>
</table>

Values are means ± SD.

\( \Delta \) = post- minus pre-bronchodilator change.

\( a, b, c, d \) means with different letters are significantly different from each other after Bonferroni adjustment for multiple comparisons (p < 0.05).
Using the ATS criteria of at least a 12% and 200 mL improvement in FEV₁ (31), the frequency of a positive response was 22.6%, 28.6% and 16.7% in the GOLD I, II and III/IV subgroup, respectively. The frequency of a positive bronchodilator response assessed by an improvement of at least 10%pr in each lung volume measurement across GOLD stages is shown in Figure 3b; again, there were fewer FEV₁ responders in the GOLD III/IV subgroup. The frequency of a positive RV response was greater than for any other lung volume within each GOLD stage subgroup, but increased progressively across GOLD stages (p < 0.0005). The frequency of a positive response determined by spirometry alone or in combination with plethysmographically-determined lung volumes is shown in Figure 4. By considering changes in SVC and/or RV in addition to FEV₁, a larger proportion of each GOLD subgroup showed a positive response to a bronchodilator, especially in GOLD stage III/IV. Reductions in sRaw by at least 10%predicted were seen in 84, 86 and 85% of subjects in GOLD I, II and III/IV, respectively.

**DISCUSSION**

The main findings of this study were as follows: 1) RV, FRC and TLC were significantly increased above predicted values in GOLD I; by contrast, VC and IC were largely preserved; 2) for the whole group, the relation between increasing airflow obstruction and decreasing VC and IC was linear, whereas indices of lung hyperinflation increased exponentially; 3) reduced air trapping (reduced RV) was the most consistent response to a bronchodilator across severity subgroups.

The unique features of this database are the inclusion of a large population who met the criteria for mild airway obstruction and the availability of reliable pre- and post- bronchodilator plethysmographic lung volumes. Given that these patients were
Figure 4. The frequency of a significant bronchodilator response (change of at least 10% predicted) is shown when only spirometric measurements are taken into account (FEV₁ alone, FVC alone or combination of FEV₁ and FVC) (top). By considering plethysmographic lung volume (RV and SVC) improvements in addition to spirometric FEV₁, greater rates of reversibility were uncovered (bottom). When volumes were taken into account, the frequency of a positive bronchodilator response increased with worsening GOLD stage.

referred to a specialized pulmonary unit for assessment, it is reasonable to assume that respiratory symptoms were present in the majority. The three subgroups stratified by GOLD criteria were well matched for age and height and had similar sex representation (i.e., 30–40% female). We validated our pulmonary function normative reference values in a control group of age- and height-matched non-smokers. Plethysmographic lung volumes in our control group were well within the normal range as predicted for the reference population, whereas spirometric volume measurements in the control sample tended to exceed the predicted normal values.

Mild airway obstruction

Individuals fitting GOLD I criteria (average post-bronchodilator FEV₁ of 93% predicted) had evidence of significant respiratory impairment which included increased lung hyperinflation, increased specific airway resistance (to 250% predicted) and reduced mid-volume expiratory flow rates (to 39% predicted) (all pre-bronchodilator values). RV was 0.73 or 35% above the predicted value, on average. The presence of an increased RV signifies increased air trapping due to enhanced airway closure during full expiration.

There is no consensus with respect to a definition of air trapping but a RV exceeding the predicted normal values by more than 20% is generally thought to be significant. A greater than normal RV has previously been reported in our own studies in GOLD I patients (9, 10), as well as in an earlier (1966) Canadian study in younger male smokers who had symptoms of chronic bronchitis (32). Not surprisingly, the increased RV correlated well with increased airway resistance and inversely with other measures of reduced expiratory flow rates.

FRC was similarly increased by an average of 0.75 or 19% above predicted normal in this group. In numerical terms, the increase in FRC was mainly explained by the increase in RV with preservation of ERV. Increased FRC values correlated inversely with FEV₁. Mechanistically, it could not be determined whether the increased FRC was due to the effects of increased lung compliance or to heterogeneous alterations in the mechanical time constants for gas emptying, or both. An earlier physiological study showed that smokers with COPD with preserved FEV₁ and FVC had measurable increases in static lung compliance (7). It is therefore conceivable (but unproven) that alteration of the elastic properties of the lung contributed to the consistent increases in TLC and FRC that were present in the GOLD I group.

In keeping with previous physiological studies (9, 10), the VC and IC in the GOLD I group were not reduced in the face of consistent increases in RV and FRC, respectively. This was explained by the accompanying increase in TLC. Derived ratios...
Thus, improvement in FEV\textsubscript{1} was more likely in those fitting (FEV\textsubscript{1}/%predicted) and decreasing VC and IC (all post-fact that FEV\textsubscript{1} gives little information about the physiological TLC-V A difference. The disparity between worsening spirom-tandem with sharper increases in sRaw and increases in the RV and related volume components rise more precipitously in arterial O2 tension gradient occur in the majority of patients with mild COPD (34, 35).

**The continuum of lung hyperinflation**

Relations between increasing airway obstruction (FEV\textsubscript{1}/%predicted) and decreasing VC and IC (all post-bronchodilator) were linear in this population. By contrast, the relations between increasing airway obstruction and increasing RV, FRC and TLC were exponential. Thus, there was a disproportionate increase in indices of lung hyperinflation as FEV\textsubscript{1} and VC worsened to a critically reduced value. In general, these data support the conclusion that progressive decline in FEV\textsubscript{1} in part reflects the concomitant reduction in VC as a result of an increased RV.

However, it seems that at the extremes of airway obstruction, RV and related volume components rise more precipitously in tandem with sharper increases in sRaw and increases in the TLC-VA difference. The disparity between worsening spirometry and increasing hyperinflation is not surprising given the fact that FEV\textsubscript{1} gives little information about the physiological determinants of air trapping such as peripheral airway function, the heterogeneity of mechanical time constants within the lungs and breathing pattern (36, 37).

**Bronchodilator reversibility of lung hyperinflation**

The pattern of reversibility varied across severity subgroups. Thus, improvement in FEV\textsubscript{1} was more likely in those fitting GOLD I criteria than those with more severe airway obstruction. Additional measurements of change in static lung volumes following bronchodilator therapy added little to evaluation of bronchodilator efficacy in those with mild airway obstruction. Among all lung volume components, the greatest effect (in terms of effect size and responder rate) was reduction of RV. This was true regardless of GOLD stage. RV changes correlated inversely with changes in FEV\textsubscript{1} and FVC across all three groups. The fact that FEV\textsubscript{1} mainly changed in proportion to changes in VC supports the idea that lung volume recruitment as a result of reduced RV is an important contributor to improved expiratory flow rates.

sRaw consistently decreased after bronchodilator in the major-ity of subjects in all GOLD groups and was correlated with change in RV. The magnitude of this change fell within one stan-dard deviation of the mean across groups, therefore, the clinical significance of this improvement is unclear.

Incremental decrements in FRC and reciprocal increases in IC also occurred as GOLD severity increased. Consistent with results of previous studies (12, 29), the largest lung volume de-flation effect was seen in those with the most severe resting lung hyperinflation. In GOLD III/IV, the majority (64%) showed a significant volume reduction response while fewer in this group had an FEV\textsubscript{1} response, i.e., 5% and 17% by ERS and ATS criteria, respectively. The true magnitude of bronchodilator reversibility may have been underestimated in our study due to the fact that only a single beta2-agonist bronchodilator was used and that there was a relatively short period of withdrawal of any long-acting bronchodilators (12 hours) prior to testing. How-ever, the disparity in flow versus volume responses is striking and indicates that important improvements in the mechanical time constants for lung emptying may occur independently of change in FEV\textsubscript{1}. Pharmacological lung volume reduction of the magnitude seen in GOLD stages II-IV is likely important but the clinical relevance of smaller such changes in GOLD I is less certain (10).

**Limitations**

We utilized a hospital database consisting exclusively of Caucasians where information on smoking history, respiratory symptoms, comorbidities, medications and healthcare utilization was not available. Therefore, the generalizability of our re-sults to a broader population of patients with COPD is unclear. However, our study sample is representative of the population of older individuals with airway obstruction that is not fully revers-ible who seek pulmonary subspecialist care. We used GOLD fixed ratio spirometric criteria for airway obstruction which may lead to over-diagnosis of COPD in the elderly (38,39). However, corroborating evidence of increased air trapping, increased air-way resistance and configurational changes in the expiratory flow-volume loop (all referenced to an age-matched control group) suggest the presence of respiratory impairment beyond the effects of healthy aging in the GOLD I subgroup.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

The novel findings of this study were as follows. Individuals with mild airway obstruction had relatively preserved vital and inspiratory capacities but showed consistent evidence of increased airway resistance and air trapping. This is the first population study to demonstrate an exponential relation between worsening airflow obstruction and indices of lung hyperinflation. The most consistent physiological improvement following acute bronchodilator therapy across GOLD stages was reduced RV. Collectively, these results provide new insights into the possible course of physiological deterioration in COPD and prompt the question of whether pharmacological reduction...
of air trapping in patients with milder airway obstruction is clinically beneficial.

ACKNOWLEDGMENTS

The authors wish to acknowledge the pulmonary function laboratory staff Cathy Muir (RRT, RCPT(P)), Denis Faubert (B.Sc., RRT) and Robin McHardy (RCPT(P)) for their careful attention to detail when conducting the tests reported as part of this study.

Declaration of interest

The authors report no conflicts of interest related to this manuscript. The authors alone are responsible for the content and writing of the paper.

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