Early COPD patients with lung hyperinflation associated with poorer lung function but better bronchodilator responsiveness

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Background: It is unknown whether aggressive medication strategies should be used for early COPD with or without lung hyperinflation. We aimed to explore the characteristics and bronchodilator responsiveness of early COPD patients (stages I and II) with/without lung hyperinflation.

Methods: Four hundred and six patients with COPD who performed both lung volume and bronchodilation tests were retrospectively analyzed. Residual volume to total lung capacity >120% of predicted values indicated lung hyperinflation. The characteristics and bronchodilator responsiveness were compared between the patients with and without lung hyperinflation across all stages of COPD.

Results: The percentages of patients with lung hyperinflation were 72.7% in the entire cohort, 19.4% in stage I, 68.5% in stage II, 95.3% in stage III, and 100.0% in stage IV. The patients with lung hyperinflation exhibited poorer lung function but better bronchodilator responsiveness of both forced expiratory volume in 1 second and forced vital capacity than those without lung hyperinflation during early COPD (r=2.21–5.70, P=0.000–0.029), especially in stage I, while age, body mass index, smoking status, smoking history, and disease duration were similar between the two subgroups in the same stages. From stages I to IV of subgroups with lung hyperinflation, stage I patients had the best bronchodilator responsiveness. Use of bronchodilator responsiveness of forced vital capacity to detect the presence of lung hyperinflation in COPD patients showed relatively high sensitivities (69.5%–75.3%) and specificities (70.3%–75.7%).

Conclusion: We demonstrated the novel finding that early COPD patients with lung hyperinflation are associated with poorer lung function but better bronchodilator responsiveness and established a simple method for detecting lung hyperinflation.

Keywords: GOLD I, GOLD II, RV/TLC, bronchodilation test

Introduction

COPD is a global disease with increasing morbidity, disability, and burden.1,2 A notable characteristic of COPD is the persistent airflow limitation, which usually develops progressively.1 The annual rates of decline in forced expiratory volume in 1 second (FEV₁) in patients with early COPD (stages I and II) are more rapid than those in patients with stages III and IV COPD.3–5 For early stable COPD, the Global initiative for chronic Obstructive Lung Disease (GOLD) recommends regular and aggressive pharmacological treatment only for patients with high level of symptoms.1 However, drug interventions during early COPD that depend on subjective symptoms may not be sufficient, while most patients do not visit hospitals or clinics until they have developed...
more severe degree of COPD by the time the diagnosis is made. To achieve early COPD intervention, especially during GOLD stage I, objective “markers” for aggressive medication strategies should be taken into account.

In a previous study, the indices of lung hyperinflation increased exponentially across GOLD stages, resulting in increased dyspnea and limitation of exercise capacity for patients with COPD. Moreover, static hyperinflation is an independent predictor of frequent exacerbations and even mortality in patients with COPD. Patients with greater resting lung hyperinflation showed more bronchodilator-induced volume deflation effects. Given the earlier associations, considerable interest exists in evaluating the clinical utility of lung hyperinflation as objective “marker” in COPD. However, it is unknown whether aggressive medication strategies should be used during early COPD (particularly for GOLD stage I) with or without lung hyperinflation. In addition, when considering COPD management in primary care settings, simple methods that do not use advanced equipment and complex technology to detect lung hyperinflation should be established.

Therefore, the purposes of the present study were a) to explore the characteristics and bronchodilator responsiveness of early COPD patients with or without lung hyperinflation and b) to test the feasibility of using bronchodilator responsiveness to detect lung hyperinflation in patients with early COPD.

Methods

Patients

This retrospective study included 406 stable patients with COPD first diagnosed by pulmonary physicians using GOLD definition in the First Affiliated Hospital of Guangzhou Medical University from January 2011 to June 2015. COPD patients were aged ≥40 years, had been evaluated by using both lung volume and bronchodilation tests, and had postbronchodilator FEV1/forced vital capacity (FVC) values <0.70. Patients were excluded if they had experienced a respiratory infection or an exacerbation of COPD within the last 4 weeks, had a history of pulmonary resection or asthma, used supplemental oxygen for >12 hours per day, or had significant diseases other than COPD that might influence either the results of the study or the patient’s ability to perform tests. The stages of COPD conform to GOLD guidelines: GOLD stage I, predicted FEV1 value (FEV1%pred) ≥80%; GOLD stage II, 50% ≤FEV1%pred < 80%; GOLD stage III, 30% ≤FEV1%pred < 50%; and GOLD stage IV, FEV1%pred < 30%.

Written informed consent of pulmonary function test (PFT) was obtained from all patients prior to the test, and the study protocol was approved by the First Affiliated Hospital of Guangzhou Medical University Ethics Committee. All patient information was kept confidential.

Pulmonary function test

The PFT equipment (Jaeger Masterscreen Body, BD, Franklin Lakes, NJ, USA; Cosmed PFT Quark, COSMED, The Metabolic Company, Rome, Italy) met the criteria of the American Thoracic Society and the European Respiratory Society. Calibration checks were performed daily prior to all tests and validated that the devices were within the calibration limits. Patients were required to refrain from the use of short- and long-acting bronchodilators (for ≥6 and ≥24 hours, respectively), short- and long-acting theophylline (for ≥24 and ≥48 hours, respectively), antileukotrienes (for ≥48 hours), smoking, exercise, and tea/coffee (for ≥4 hours).

All lung volume and bronchodilation tests were conducted by skilled and certified doctors/technicians according to American Thoracic Society and the European Respiratory Society guidelines. For the lung volume test, body plethysmography or multiple-breath nitrogen washout was performed. Then, spirometry was performed before and 20–30 minutes after administration of 400 μg of salbutamol via metered dose inhaler. The change in FEV1 was expressed as 1) the percentage change relative to baseline (ΔFEV1%baseline), 2) the absolute change in the percentage of the predicted value (ΔFEV1%pred), and 3) the absolute change relative to baseline (ΔFEV1). The change in FVC was expressed in a similar manner. Predicted values of lung volume and spirometry were calculated from the reference equations published by Stocks et al and Zheng and Zhong, respectively. An abnormal ratio of residual volume to total lung capacity (RV/TLC) was considered pathological. RV/TLC values >120% of predicted values indicated lung hyperinflation.

Statistical analysis

Data were analyzed by using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). The characteristics of the study population are reported as mean ± standard deviation or as counts and percentages unless otherwise specified. Group differences between the presence and absence of lung hyperinflation within the entire cohort and each GOLD stage were explored using an unpaired t-test, a Mann–Whitney U-test, or a χ²-square test where appropriate. Comparisons across GOLD stages were analyzed using analysis of variance.
Pearson’s correlation was used to evaluate the relationships between the RV/TLC%pred and bronchodilator responsiveness of the FVC and FEV1. Multivariate logistic regression analyses with age, sex, body mass index (BMI), technology of lung volume test, smoking status, self-reported smoking history, self-reported COPD duration, GOLD stage, ΔFVC, and ΔFEV1 were used to determine the association between these characteristics and the presence or absence of lung hyperinflation. Receiver operating characteristic curves were generated for selected cutoff values of bronchodilator responsiveness to detect lung hyperinflation. *P*-values <0.05 were considered significant in all analyses.

**Results**

**Population characteristics**

Of the 406 patients in the present study, 369 (90.9%) were males and 37 (9.1%) were females. The distribution of COPD stages was 16.5% in GOLD stage I, 39.9% in GOLD stage II, 31.3% in GOLD stage III, and 12.3% in GOLD stage IV (Table 1). The mean age, sex, and smoking status were similar within each GOLD stage subgroup, whereas greater self-reported smoking history (pack-year); longer self-reported COPD duration; higher RV%pred, TLC%pred, and RV/TLC%pred; and lower BMI, FVC%pred, FEV1%pred, and FEV1/FVC% were showed in the greater severity subgroup (F=2.89–972.11, *P*=0.000–0.035).

**Characteristics and bronchodilator responsiveness of patients with or without lung hyperinflation**

The percentages of patients with lung hyperinflation were 72.7% in the entire cohort, 19.4% in GOLD stage I, 68.5% in stage II, 95.3% in stage III, and 100.0% in stage IV (Table 1). Although patients with lung hyperinflation had lower BMIs and reported a greater smoking history and longer disease duration than those without lung hyperinflation in the entire cohort (|*=|2.02–4.30, *P*=0.000–0.044), no significant differences were found in terms of mean age, sex, BMI, smoking status, smoking history, and disease duration between patients with and without lung hyperinflation in GOLD stages I and II. Nevertheless, patients with lung hyperinflation had lower FVC%pred and FEV1%pred and higher RV%pred, TLC%pred, and RV/TLC%pred values than those without lung hyperinflation in GOLD stages I and II (|*=|2.54–17.28, *P*=0.000–0.013).

Regarding the bronchodilator responsiveness of the entire cohort (Table 2), patients with lung hyperinflation showed significant improvement in FVC compared to those without hyperinflation (0.27±0.21 L vs 0.09±0.15 L, *t*=9.88, *P*<0.001), but no significant improvement in FEV1 (0.14±0.12 L vs 0.13±0.10 L, *t*=1.28, *P*=0.201). However, the improvements of both FVC and FEV1 in patients with lung hyperinflation were significantly higher than those in patients without lung hyperinflation in GOLD stages I (0.32±0.20 L vs 0.08±0.15 L, *t*=4.83, *P*<0.001; 0.30±0.18 L vs 0.13±0.11 L, *t*=3.15, *P*=0.007, respectively) and II (0.26±0.22 L vs 0.09±0.15 L, *t*=5.70, *P*<0.001; 0.17±0.11 L vs 0.13±0.10 L, *t*=2.21, *P*=0.029, respectively). Among the patients with lung hyperinflation across each COPD stage, subgroup differences existed for FEV1 improvement (*F*=19.72, *P*<0.001), but not for FVC improvement (*F*=0.85, *P*=0.469). In addition, the present study showed no difference in the poor bronchodilator responsiveness between GOLD stages I and II without lung hyperinflation (|*=|0.08–1.56, *P*=0.121–0.940).

**Logistic regression for patients with lung hyperinflation**

The variables from the multivariate logistic regression model are listed in Table 3. The odds for meeting lung hyperinflation criteria tended to be higher for females than males. The model also showed that higher odds of lung hyperinflation were associated with increased COPD severity. The ΔFVC was the most significant factor, and patients with greater ΔFVC tended to exhibit higher odds of lung hyperinflation. However, age, BMI, technology of lung volume test, smoking status, smoking history, disease duration, and ΔFEV1 were not significant in the logistic regression analysis.

**Cutoff values of bronchodilator responsiveness used to detect lung hyperinflation**

Linear relationships were observed between RV/TLC%pred and ΔFVC (*r*=0.386, *P*<0.001), ΔFVC%baseline (*r*=0.495, *P*<0.001), and ΔFVC%pred (*r*=0.378, *P*<0.001) (Figure 1). The relationships between RV/TLC%pred and ΔFEV1 (*r*=-0.002, *P*=0.975) and ΔFEV1%pred (*r*=-0.012, *P*=0.806) were poor, except for RV/TLC%pred and ΔFEV1%baseline (*r*=0.362, *P*<0.001).

The area under the receiver operating characteristic curve (AUC) for the entire cohort for detecting lung hyperinflation with ΔFVC%baseline was highest (0.811), followed by ΔFVC and ΔFVC%pred, with AUCs of 0.766 and 0.767, respectively (Figure 2). In addition, the AUCs of the GOLD stages I–III were 0.838, 0.774, and 0.756, respectively, when using ΔFVC%baseline to predict lung hyperinflation, indicating that earlier stages exhibited larger AUCs.
### Table 1 Subject characteristics for each COPD stage

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=406)</th>
<th>GOLD I (n=67)</th>
<th>GOLD II (n=162)</th>
<th>GOLD III (n=127)</th>
<th>GOLD IV (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LH (72.7%)</td>
<td>NLH (27.3%)</td>
<td>Total</td>
<td>LH (68.5%)</td>
<td>NLH (31.5%)</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>92.8</td>
<td>90.2</td>
<td>90.9</td>
<td>76.9</td>
<td>90.7</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.8±7.7</td>
<td>66.3±8.8</td>
<td>65.2±8.0</td>
<td>67.2±6.6</td>
<td>66.2±8.1</td>
</tr>
<tr>
<td>Smoking status</td>
<td>12.9/54.2/32.9</td>
<td>10.8/46.8/24</td>
<td>12.3/52.2/25.5</td>
<td>15.4/53.8/30</td>
<td>11.1/40.7/29</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/pred</td>
<td>77.3±7.3</td>
<td>67.6±6.9</td>
<td>77.0±7.1</td>
<td>76.8±6.9</td>
<td>77.0±7.1</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>75.2±18.1*</td>
<td>51.0±21.9</td>
<td>71.7±7.4</td>
<td>89.6±12.4</td>
<td>86.2±13.6</td>
</tr>
<tr>
<td>rV/TLC, %pred</td>
<td>47.6±16.9</td>
<td>80.3±18.0</td>
<td>56.6±22.5</td>
<td>84.6±3.6</td>
<td>95.2±10.9</td>
</tr>
<tr>
<td>rV/TLC, %pred</td>
<td>44.0±11.4</td>
<td>56.8±9.0</td>
<td>47.5±12.2</td>
<td>58.4±7.4</td>
<td>62.3±4.8*</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>44.8±11.7</td>
<td>59.1±8.9</td>
<td>48.7±12.7</td>
<td>61.9±7.2</td>
<td>64.5±4.0</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/prebronchodilator, %pred</td>
<td>160.0±39.5</td>
<td>100.6±17.9</td>
<td>143.7±43.9</td>
<td>143.2±22.1</td>
<td>99.8±19.5</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>105.2±16.9</td>
<td>96.3±11.1</td>
<td>102.8±16.0</td>
<td>106.9±9.3</td>
<td>99.0±10.3*</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/prebronchodilator, %pred</td>
<td>151.6±20.1</td>
<td>104.3±12.3</td>
<td>138.7±27.9</td>
<td>133.1±9.5</td>
<td>100.1±13.4</td>
</tr>
</tbody>
</table>

**Notes:** Data are presented as mean ± standard deviation or percentages. *P<0.05, **P<0.01, ***P<0.001 compared to the lung hyperinflation group in the same COPD stage. – Represents no data.

**Abbreviations:** BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; %pred, percentage of predicted value; RV, residual volume; TLC, total lung capacity; LH, lung hyperinflation; NLH, not lung hyperinflation.
Table 2 Bronchodilator responsiveness of FVC and FEV₁ for each COPD stage

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=406)</th>
<th>GOLD I (n=67)</th>
<th>GOLD II (n=162)</th>
<th>GOLD III (n=127)</th>
<th>GOLD IV (n=50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFVC, L</td>
<td>0.72±0.21</td>
<td>0.22±0.22</td>
<td>0.20±0.18</td>
<td>0.22±0.22</td>
<td>0.22±0.22</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁, L</td>
<td>0.14±0.11</td>
<td>0.14±0.11</td>
<td>0.14±0.11</td>
<td>0.15±0.14</td>
<td>0.14±0.11</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁, %pred</td>
<td>5.8±4.4</td>
<td>5.5±4.3</td>
<td>5.6±4.3</td>
<td>5.8±4.3</td>
<td>5.5±4.3</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁/FVC, %</td>
<td>0.8±3.5</td>
<td>1.2±3.4</td>
<td>1.3±3.4</td>
<td>1.2±3.4</td>
<td>1.2±3.4</td>
<td></td>
</tr>
</tbody>
</table>

Table notes: Data are presented as mean ± standard deviation or percentages. *P<0.05, **P<0.01, ***P<0.001 compared to the lung hyperinflation group in the same COPD stage. – Represents no data. P-value, compared among the total groups of GOLD I to IV.

Abbreviations: FVC, forced expiratory volume in 1 second; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; Δ, absolute change relative to baseline; %baseline, percentage change relative to baseline; Δ%pred, absolute change in percentage of the predicted value; LH, lung hyperinflation; NLH, not lung hyperinflation.

Discussion

The main findings of the present study were as follows: 1) Early COPD patients with lung hyperinflation showed poorer lung function but better bronchodilator responsiveness than those without lung hyperinflation. 2) Bronchodilator responsiveness showed similar patterns between the two subgroups for the same stage of COPD: patients with lung hyperinflation exhibited greater bronchodilator responsiveness in COPD stages 1 to 3. 3) There was no difference in the distribution of bronchodilator responsiveness of FVC between GOLD I and II patients. The cutoff values with the best sensitivity and specificity for each functional variable were selected according to the receiver operating characteristic analysis: 0.15 L of ARVC and 1.5% of FEV₁/FVC to detect a sensitivity of 75% and a specificity of 75%. 4) ARVC and FEV₁/FVC may serve as objective markers for aggressive pharmacological intervention for early COPD, especially for GOLD stage I, which comprises subjective assessments...

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Table 3 Multivariate logistic regression analysis of patients with lung hyperinflation

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.207 (0.067–0.636)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age</td>
<td>0.996 (0.955–1.038)</td>
<td>0.844</td>
</tr>
<tr>
<td>BMI</td>
<td>0.958 (0.865–1.061)</td>
<td>0.411</td>
</tr>
<tr>
<td>Technology of lung volume test</td>
<td>1.206 (0.581–2.503)</td>
<td>0.616</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.957 (0.533–1.655)</td>
<td>0.874</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.006 (0.992–1.019)</td>
<td>0.409</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.052 (0.999–1.106)</td>
<td>0.052</td>
</tr>
<tr>
<td>GOLD stage</td>
<td>9.852 (3.368–18.082)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔFVC</td>
<td>144.836 (17.755–1,181.484)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔFEV₁</td>
<td>7.840 (0.227–270.436)</td>
<td>0.254</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; OR, odds ratio; Δ, absolute change relative to baseline.

Figure 1 Scatter diagrams for RV/TLC%pred versus ΔFVC, ΔFVC%baseline, ΔFVC%pred, and ΔFEV₁.

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; %pred, percentage of predicted value; Δ, absolute change relative to baseline; Δ%baseline, percentage change relative to baseline.
Early COPD patients with lung hyperinflation

Limitations

Some limitations were present in our study. As a retrospective study, we could not record additional clinical data from the COPD patients, such as modified medical research council scores, COPD assessment test scores, and the number of exacerbation events during the previous year. The multiple-breath N₂ washout was performed in 78.6% of patients, while the lung volume measured by body plethysmography differs with that measured by multiple-breath N₂ washout in COPD, the more, the higher grade of obstruction. However, the present study focused on early COPD that with lower grade of obstruction, and the technology of lung volume test did not show any significance in the logistic regression analysis for detecting lung hyperinflation. In addition, the number of patients with GOLD stage I and female patients was relatively small, although they did reflect the reality of COPD management in the People’s Republic of China. Nevertheless, we found evidence that lung hyperinflation in patients with early COPD is associated with poorer lung function but better bronchodilator responsiveness. These limitations have been considered in our upcoming study, which prospectively focuses on the long-term treatment effects and clinical outcomes of patients with or without lung hyperinflation in early COPD, especially in GOLD stage I.

Conclusion

This study provided novel findings regarding the presence of lung hyperinflation in COPD patients, which may serve
as an objective “marker” for aggressive pharmacological intervention for early COPD. In addition, the present study established a simple method using the bronchodilator responsiveness of FVC to detect lung hyperinflation.

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Author contributions
JZ is the guarantor of the paper, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. WJ contributed to study design, quality control, acquisition of the data, statistical analysis, and revising of the manuscript. CC contributed to quality control, acquisition of the data, statistical analysis, and drafting of the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All the authors have read and approved the final manuscript.

Disclosure
The authors report no conflicts of interest in this work.

References