Assessment of Emphysema in COPD*

A Functional and Radiologic Study

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Objectives: A combination of functional measurements reflecting a decrease in maximum flow, a degree of lung hyperinflation, the relationship between maximum inspiratory and expiratory flows, bronchodilator response, and diffusing capacity of the lung for carbon monoxide (DLCO) was used to quantify the extent of emphysema, as assessed by high-resolution CT (HRCT) scanning.

Design: Forced inspiratory and expiratory spirometry, lung volumes, reversibility test, and single-breath diffusing capacity were assessed before and after inhaling albuterol, 200 μg. Relationships between lung function variables and emphysema extent, as determined by HRCT scanning, were tested by univariate and multivariate analyses.

Subjects: Thirty-nine COPD outpatients with moderate-to-severe obstruction.

Measurements and results: Emphysema extent, as assessed by HRCT scanning, ranged from 18 to 70%. All of the lung function parameters that were studied, except for the change in FEV₁ percent predicted after salbutamol inhalation, correlated significantly with the extent of emphysema (r² range, 0.19 to 0.44). Functional residual capacity, forced expiratory flow at 50% of FVC/forced inspiratory flow at 50% of FVC, DLCO/alveolar volume ratio, and bronchodilator-induced change in FEV₁/FVC ratio were the only variables retained by stepwise multiple regression analysis. The multiple regression model explained 71% of the variability of emphysema extent measured by HRCT scanning.

Conclusions: The combination of lung function measurements reflecting lung hyperinflation, bronchial collapsibility, lung diffusing capacity, and bronchodilator response provides a good estimate of the extent of emphysema, as evaluated by HRCT scanning. These data suggest that pulmonary function tests are useful in assessing and monitoring parenchymal damage in COPD patients.

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Key words: bronchodilation; diffusing capacity; high-resolution CT; lung volumes; spirometry

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; FEF₅₀ = forced expiratory flow at 50% of FVC; FIF₅₀ = forced inspiratory flow at 50% of FVC; FRC = functional residual capacity; HRCT = high-resolution CT; RV = residual volume; TGV = thoracic gas volume; TLC = total lung capacity; VA = alveolar volume

Airflow obstruction in COPD patients is believed to be largely secondary to airway damage and remodeling, while emphysema is considered to play only a minor role.¹ As a consequence, the pharmacologic interventions recommended for COPD patients¹ are uniquely aimed at increasing airway caliber and reducing airway inflammation. This approach is also justified by the present unavailability of drugs that are able to modify lung parenchymal properties.² However, it can be expected that new drugs will be developed in the future in an attempt to specifically treat airway or parenchymal damage. If this will be the case, the variability of response to treatments could be reduced by assessing patients for the presence and extent of emphysema.

High-resolution CT (HRCT) scanning is considered to be a sensitive technique for detecting and quantifying pulmonary emphysema in vivo,³ but it may not be easy to obtain in many centers and is not suitable for follow-up. Studies attempting to relate pulmonary function measurements to HRCT scans...
findings have been disappointing, as correlations explaining no more than one fourth to one half of variability were generally found,4 possibly because none of the parameters recommended for lung function testing in COPD patients is uniquely sensitive to the pathologic features of emphysema. Maximum expiratory flow is reduced in emphysema because of the loss of lung elastic recoil, but it also may be decreased in intrinsic airway obstruction. The diffusing capacity of the lung for carbon monoxide (DLCO) is reduced in emphysema patients because of the loss of alveolar-to-capillary surface, but it also may be decreased due to very severe airway obstruction.

In addition to the reduction of maximal expiratory flow, which is generally assessed by FEV1, other mechanical abnormalities may reflect the loss of lung elastic recoil. Among these abnormalities are lung hyperinflation,5 airway collapsibility,6 and altered airway-to-parenchyma interdependence.7–9 The aim of the present study was to examine to what extent a combination of noninvasive pulmonary function measurements reflecting the above features is capable of quantifying the presence of emphysema in COPD subjects in comparison with HRCT scanning.

**MATERIALS AND METHODS**

**Subjects**

Thirty-five male subjects and 4 female subjects affected by COPD10 took part in this study (Table 1). All subjects were smokers or past smokers; 36 subjects had a history of chronic cough and phlegm, and 20 subjects had reported dyspnea. All subjects were required to abstain from receiving short-acting bronchodilators for at least 12 h, to be in a stable clinical condition, and not to have experienced respiratory exacerbations in the previous month. The study was approved by the local ethics committee, and informed consent was obtained from all subjects.

**Table 1—Anthropometric and Pulmonary Function**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>64 ± 7</td>
<td>48–80</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167 ± 6</td>
<td>155–182</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>47 ± 16</td>
<td>21–72</td>
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<tr>
<td>FVC, % predicted</td>
<td>80 ± 19</td>
<td>33–108</td>
</tr>
<tr>
<td>FEF50, L/s</td>
<td>0.57 ± 0.30</td>
<td>0.16–1.37</td>
</tr>
<tr>
<td>FEF50, L/s</td>
<td>3.29 ± 1.01</td>
<td>1.75–5.41</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>144 ± 28</td>
<td>95–203</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>153 ± 39</td>
<td>78–241</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>115 ± 13</td>
<td>90–139</td>
</tr>
<tr>
<td>FEV1 change, %</td>
<td>8 ± 6</td>
<td>–1–26</td>
</tr>
<tr>
<td>FEV1/FVC change, %</td>
<td>–1 ± 4</td>
<td>–11–12</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>65 ± 19</td>
<td>29–105</td>
</tr>
<tr>
<td>DLCO/VA</td>
<td>67 ± 17</td>
<td>30–90</td>
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</table>

*After salbutamol administration.

**Pulmonary Function**

On the first day of the study, a complete lung function test was obtained before and 30 min after inhalation of 200 μg of salbutamol (Autobox V6200 and V˙max 22 system; SensorMedics Corporation; Yorba Linda, CA).

At baseline and after salbutamol administration, FVC and FEV1 were measured according to the American Thoracic Society guidelines.11 The change in FEV1 after salbutamol administration (expressed as percentage of predicted values) was taken as the traditional index of bronchodilation. As it is well-known,7–9 a large proportion of patients with emphysema show an increase in FVC despite minimal or no change in FEV1. This indisputable sign of bronchodilation is called isolated volume response. Thus, the change in the FEV1/FVC ratio after salbutamol therapy (ie, post-FEV1/FVC % – pre-FEV1/FVC %) was taken as an index of relative response in terms of flow and volume.

Forced expiratory flow measured at 50% of FVC (FEF50) and forced inspiratory flow measured at 50% of FVC (FIF50) were taken on the flow-volume loops showing the best combination of FVC and FEV1, and superimposable inspiratory flows. The FEF50/FIF50 ratio was taken as an index of airway collapsibility.

Thoracic gas volume (TGV) was measured by body plethysmography, with the subjects panting against a closed shutter at a frequency slightly < 1 Hz and their cheeks supported by their hands. Total lung capacity (TLC) was obtained as the sum of TGV and linked inspiratory capacity. Residual volume (RV) was the difference between TLC and a relaxed vital capacity. Functional residual capacity (FRC) was obtained that were corrected for any difference between the volume at which the shutter was closed and the average end-expiratory volume of the four preceding regular tidal breaths. Predicted values for spirometry and lung volumes are from Quanjer et al.12

DLCO and alveolar volume (VA) were measured at least in duplicate, as described by Huang and Machty.13 Predicted values are derived from Cotes et al.14

**HRCT Imaging**

A third-generation, continuous-rotation CT scanner with volume acquisition extendable to 24 s (Somaton Plus; Siemens; Erlangen, Germany) was used. The quantitative evaluation of emphysema was based on three scans of 2-mm thick sections that were acquired with 200-mA tube current, and were obtained at the levels of the aortic arch, tracheal carina, and pulmonary veins while the patient was holding his breath at RV. By using appropriate software (Siemens) and the “density mask” method,15 the percentage of pixels with a density of < –900 Hounsfield units at full expiration was calculated.16

**Statistical Analysis**

The normality of the data distribution was assessed by the Shapiro-Wilks test. Relationships between variables were tested by linear regression analysis and Pearson correlation coefficient. The simultaneous effects of lung function parameters were analyzed by multiple linear regression analysis, with emphysema extent determined by HRCT scan as the dependent variable and independent variables selected by a stepwise procedure. The independent variables were FEV1 (percentage of predicted), FRC (percentage of predicted), TLC (percentage of predicted), RV (percentage of predicted), RV/TLC ratio, DLCO (percentage of predicted), DLCO/VA ratio, FEF50/FIF50 ratio, salbutamol-induced change in FEV1 (percent predicted), and salbutamol-induced change in FEV1/FVC ratio. Values of p < 0.05 were considered to be statistically significant. All tests were two-sided using a statistical software package (Statistica for Windows, version 6; StatSoft; Tulsa, OK). Data are presented as the mean ± SD.
RESULTS

All subjects had moderate-to-severe airflow obstruction (Table 1), and most of them also had lung hyperinflation (i.e., increase in FRC), gas trapping (i.e., an increase in RV), and reduction of DLCO. In all subjects, FEF50 values were always remarkably less than the FIF50 values, with the ratio FEF50/FIF50 ratio ranging from 0.1 to 0.4. The salbutamol-induced change in FEV1 ranged from -1 to +26% predicted, and the absolute change in FEV1/FVC ratio ranged from -11 to +12%.

The mean extent of emphysema determined by HRCT scan was 39 ± 12% (range, 18 to 70%) of the total lung cross-sectional area, and was correlated with FEV1, FRC, TLC, RV, and DLCO, with the ratios RV/TLC, FEF50/FIF50, and DLCO/VA, and with ΔFEV1/FVC ratio (Table 2). The relationships of lung function parameters with each other are reported in Table 3. The variance of emphysema extent measured by HRCT scan that was explained by each single lung function parameter ranged from 19 to 44%. A much greater proportion of emphysema extent measured by HRCT scanning was explained by the following multiple regression model with four independent variables selected by a stepwise procedure:

emphysema extent (%) = 38.5 + 0.30 × FRC − 0.30 × FEF50/FIF50 − 0.24 × DLCO/VA − 0.26 × ΔFEV1/FVC (r² = 0.71, p < 0.001)

The relationship between the model estimate and emphysema extent measured by HRCT scan is presented in Figure 1.

DISCUSSION

The main finding of this study was that a fairly large proportion of the emphysema assessed by HRCT scan was explained by a multiple regression model, including noninvasive lung function measurements reflecting lung hyperinflation, bronchial collapsibility, alveolar-to-capillary diffusion capacity, and bronchodilator response. It is well-recognized that COPD is a very inhomogeneous condition, and this is likely the major reason for the inconsistency of the results among clinical trials. It is conceivable that a better characterization of the underlying disease may help to reduce the variability of response to therapeutic interventions in COPD patients. However, the recently published guidelines of the Global Initiative for Chronic Obstructive Lung Disease consider COPD patients as a homogeneous population, at least with regard to pharmacologic treatment. Accordingly, only simple spirometry is recommended to evaluate the presence and severity of airway obstruction, while the assessment of emphysema by HRCT scan is restricted to those patients who are possible candidates for surgery. In the last few years, great attention has been paid to drugs that specifically address either airflow obstruction (e.g., phosphodiesterases inhibitors) or parenchymal damage (e.g., α1-antitrypsin augmentation therapy). From this perspective, a quantification of emphysema may help to tailor treatments to individual patients.

The use of HRCT scanning for the assessment of emphysema has some limitations. First, it may not be easy to obtain in a number of centers. Second, it exposes the patient to radiation. Third, it cannot be taken as an indisputable "gold standard" for the quantification of emphysema, as it provides correlation coefficients with lung pathology ranging from 0.7 to 0.9.17–19 Fourth, it is not suitable for follow-up. However, lung function tests are easy to obtain in most centers, but the relationships between single parameters and the extent of emphysema, determined either by pathology or HRCT scan, are rather weak.2,20–24 The present study gives an answer to the following two practical questions: whether the extent of emphysema can be assessed by lung function tests; and which measurements are useful in achieving agreement with HRCT scan data.

Lung hyperinflation is well-known as a major characteristic of emphysema patients and is regarded as reflecting the quintessential feature of this disease (i.e., the decrease in lung elastic recoil). Respiratory system mechanics predict that a decrease in lung elastic recoil should result in an increase of both FRC and TLC. In the present study, both TLC and FRC significantly correlated with the extent of emphysema as determined by HRCT scan, but only FRC was retained as being significant in the multiple regression model. As lung volume were significantly correlated, the retention of FRC only could have been an artifact due to the

Table 2—Relationship Between Functional Variables and Emphysema Extent as Assessed by HRCT Scan

<table>
<thead>
<tr>
<th>Variables</th>
<th>r Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, % predicted</td>
<td>-0.52</td>
<td>0.001</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>0.66</td>
<td>0.00001</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>0.52</td>
<td>0.001</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>0.54</td>
<td>0.0004</td>
</tr>
<tr>
<td>RV/TLC ratio</td>
<td>0.44</td>
<td>0.01</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>-0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>DLCO/VA ratio</td>
<td>-0.64</td>
<td>0.00001</td>
</tr>
<tr>
<td>FEF50/FIF50 ratio, L/s</td>
<td>-0.66</td>
<td>0.00001</td>
</tr>
<tr>
<td>FEVi change, % predicted</td>
<td>-0.29</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/FVC ratio change, %</td>
<td>-0.59</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*NS = not significant.
†After salbutamol administration.

Clinical Investigations
Airflow obstruction in COPD patients is variably due to intrinsic airway obstruction or the loss of lung elastic recoil. In the presence of emphysema, the caliber of intraparenchymal airways is expected to be much less on expiration than on inspiration because airway walls are more compressible or the tethering force of lung parenchyma is reduced. The significant inverse relationship between the \(\text{FEV}_{50}/\text{FIF}_{50}\) ratio and the extent of emphysema as assessed by HRCT scan confirms these predictions.

In our previous study, we showed that an isolated volume response to bronchodilators occurred in patients with emphysema as a result of an increase in flow, mostly occurring at low lung volumes rather than high lung volumes. This phenomenon was found to be associated with a paradoxical decrease in small airway caliber from FRC to TLC as measured by HRCT, thus reflecting an altered coupling between airways and lung parenchyma. In the present study, the significant inverse relationship between changes in \(\text{FEV}_{1}/\text{FVC}\) ratio after salbutamol administration and the extent of emphysema reflects the fact that volume responses (ie, an increase in FVC) exceeded flow responses (ie, an increase in \(\text{FEV}_{1}\)).
Finally, as abundantly documented in the literature, the more extensive the emphysema, the lower the DLco. This feature is deemed to reflect the pathologic consequences of lung hyperinflation and alveolar disruption on the vascular side.20

Other variables that were significantly correlated with the extent of emphysema were FEV1, RV, and RV/TLC ratio. Among the possible reasons for this are that the decrease in flow and the occurrence of airway closure at high lung volume is due either to a decrease in elastic recoil, as is the case in emphysema patients, or to intrinsic airway disease, as is the case in patients with chronic bronchitis.

Although the prediction formula found in this study cannot be generalized before it is tested in subjects who are different from those from whom it was generated, the clinical implications of the present findings are that a multiple regression model based on noninvasive lung function measurements provides a good estimate of the extent of emphysema in COPD patients, as assessed by HRCT scanning. In consideration of the fact that HRCT scanning exposes the patient to radiation and cannot be used repeatedly to monitor the disease, this functional approach may be particularly useful for clinical trials of new treatments for COPD.

REFERENCES