Relationship of emphysema and airway disease assessed by CT to exercise capacity in COPD

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Summary
Objective: To assess the association of emphysema and airway disease assessed by volumetric computed tomography (CT) with exercise capacity in subjects with chronic obstructive pulmonary disease (COPD).

Methods: We studied 93 subjects with COPD (Forced Expiratory Volume in 1 s [FEV1] % predicted mean ± SD 57.1 ± 24.3%, female gender = 40) enrolled in the Lung Tissue Research Consortium. Emphysema was defined as percentage of low attenuation areas less than a threshold of –950 Hounsfield units (%LAA-950) on CT scan. The wall area percentage (WA%) of the 3rd to 6th generations of the apical bronchus of right upper lobe (RB1) were analyzed. The 6-min walk distance (6MWD) test was used as a measure of exercise capacity.

Results: The 6MWD was inversely associated with %LAA-950 (r = 0.53, p < 0.0001) and with the WA% of 6th generation of RB1 only (r = 0.28, p = 0.009). In a multivariate regression model including CT indices of emphysema and airway disease that were adjusted for demographic and physiologic variables as well as brand of CT scanner, only the %LAA-950 remained significantly associated with exercise performance. Holding other covariates fixed, this model...
Introduction

A reduction in exercise capacity is frequent in subjects with chronic obstructive pulmonary disease (COPD) and is traditionally associated with impaired lung function. There is, however, increasing recognition that spirometric measures of lung function alone do not explain all the variance found in clinical measures of disease. As detailed by Reilly in his editorial to the UPLIFT study, COPD appears to be an aggregate of several unique subtypes. Given this heterogeneous population, new measures of disease such as computed tomography (CT) assessment of emphysema and airway disease are of great interest in helping to understand disease pathophysiology and standard clinical measures such as exercise capacity.

The 6-min walk distance test (6MWD) is a commonly used measure of exercise capacity in subjects with COPD. It requires minimal equipment to perform and is widely available. While CT is increasingly used to quantitatively assess both the emphysema and airway disease in COPD, studies of their contribution to exercise capacity are more limited. Gould et al. and Lee et al. reported an association between emphysema assessed by CT and exercise capacity assessed by walking tests, but the relation of airway disease to exercise capacity, however, has not been demonstrated.

Based on prior studies revealing the inverse correlation between CT airway disease and lung function, we hypothesize that CT measures of airway disease would provide complimentary information to CT measures of emphysema in predicting exercise capacity measured by 6MWD independent of lung function. We undertook this study using data from Lung Tissue Research Consortium (LTRC), a National Heart, Lung and Blood Institute initiative to characterize subjects with chronic pulmonary diseases such as COPD.

Methods

Subjects selection

The data used in this study were collected as part of the LTRC and included measures of lung function, exercise testing, and volumetric CT scanning of the chest performed prior to lung volume reduction surgery, transplantation, and resection for suspected malignancy. Subjects were evaluated for inclusion in our study if they had a diagnosis of COPD (postbronchodilator forced expiratory volume in 1 s to forced expiratory vital capacity ratio $[FEV_1/FVC] < 0.7$) and a high resolution volumetric CT scan available for quantitative analysis. Five out of the 99 patients that met the two above criteria were eliminated because of a history of chronic heart failure which has been demonstrated to influence exercise performance. A sixth subject was excluded because of a giant bulla in the right lung which resulted in mediastinal displacement. The final study cohort consisted of 93 subjects and informed consent was obtained from each participant. The study was approved by the Institutional Review Board of Brigham and Women’s Hospital (BWH).

Physiologic assessment

All subjects underwent standardized spirometric measures of lung function according to American Thoracic Society (ATS) guidelines. The postbronchodilator $FEV_1$ and $FVC$ were recorded in liters and expressed as percentages of predictive values ($FEV_1\%P$ and $FVC\%P$) using standardized prediction equations. Lung volume measurements were performed by body plethysmography. The residual volume, total lung capacity, and the residual volume to total lung capacity ratio were expressed as percentages of predicted values ($RV\%P$, $TLC\%P$ and $RV/TLC\%P$, respectively). The 6MWD was performed in a standardized manner following ATS recommendations. This test was typically performed once prior to a subject undergoing surgery. In four patients more than one walk test was taken while they were awaiting transplantation. In these cases, the walk test in closest proximity to the surgery was evaluated. Oxygen saturation ($SO_2$) was measured before and at the end of the walk test. Oxygen supplementation was titrated to achieve a resting $SO_2$ level of at least 88% prior to starting the test. The walking distance was recorded in meters.

Imaging assessment

The radiology core laboratory defined CT protocols for LTRC. CT scanners follow the American College of Radiology guidelines for accreditation (www.acr.org/accreditation/computed). Computed tomographic images were acquired in the supine position at full inflation using both General Electric (GE) and Siemens scanners. GE Protocol: 55 subjects underwent CT scanning using a GE CT scanner. Images were acquired using a 30 cm field of view (FOV) in a GE LightSpeed 16 multislice scanner using a tube voltage of 140 kVp, a tube current of 300 or 375 mA for most subjects ($n = 48$) and variable doses for the remaining subjects. Images were reconstructed using the bone algorithm at 1.25 mm slice thickness and 0.625 mm interval.

Siemens Protocol: 38 subjects underwent CT scanning by using Siemens Sensation 10 or 64 multislice scanners. Images were similarly acquired using a 30 cm FOV at 140 kVp with an automated dose modulation. Images were reconstructed...
using the b46f algorithm at 1 mm slice thickness and 0.5 mm interval.

**Emphysema and airway analysis**

Quantitative measures of emphysema for the whole lung and for airway disease were calculated using open-source software (www.airwayinspector.org). Emphysema was defined as low attenuation areas using a Hounsfield Unit (HU) threshold of $-950$ (%LAA-950). Single-slice airway measurements were collected in the apical bronchus of the right upper lobe (RB1). RB1 was chosen because its long axis is generally perpendicular to axial imaging plane and prior studies have shown measures taken at this site correlate with lung function and predict small airway dimensions assessed by histological means. Analysis was performed in the 3rd (segmental bronchus), 4th, 5th, and 6th generation. In each generation, one measurement was taken at what was judged to be the central portion of the segment of interest in an image reformatted orthogonally to the long axis of the lumen. The Phase Congruency method for airway segmentation was used to define the lumen-wall and wall-parenchymal boundaries and total airway area (Ao), airway lumen (Al), and wall area percentage (WA%) defined as $(Ao-Al)/Ao \times 100$% were measured at each point of interest.

**Statistical analysis**

Baseline characteristics are expressed as mean and SD or median and interquantile range when appropriate. Pearson’s correlation coefficients were used to assess univariate relationships between CT-based measures of airway disease and emphysema, lung function, and 6MWD. Multivariate linear regression models were created using 6MWD as the response variable and %LAA-950 and WA% of 6th generation of RB1 together as explanatory variables. WA% of 6th generation was chosen because it correlated significantly with 6MWD in univariate analysis. Adjustment was done for the following known factors that influence a subject’s exercise capacity: age, gender, body mass index (BMI), and RV/TLC ratio is an estimate of hyperinflation that has been shown that influences subject’s exercise performance. Model adjustment was also done for scanner brand and cancer status (presence or absence of malignancy on surgical pathology). The analysis was performed with SAS version 9.1 (Cary, NC). A $P$ value of 0.05 was considered statistically significant.

**Results**

Table 1 shows baseline characteristics of the study subjects. The mean FEV$_1$ was $1.6 \pm 0.7$ L (range: 0.5–3.3 L). Fifteen out of 93 (16%) subjects used supplemental oxygen for the walk test. These 15 subjects had significant lower FEV$_1$%P (mean $\pm$ SD $37.1 \pm 24.7\%$ vs $60.1 \pm 22.2\%$), lower FEV$_1$/FVC (209.2 $\pm$ 80.7 vs 151.1 $\pm$ 49.1%), shorter distance walked (193.2 $\pm$ 106.1 vs 357.7 $\pm$ 142.1 m), and higher %LAA-950 (median 42.2 [interquantile range 25–51%]) than the 78 non-oxygen users. Fifty-eight of the 93 subjects received a diagnosis of cancer. Data by cancer status is shown in Table 2.

**Association between CT emphysema, WA%, lung function, and exercise capacity**

CT indices of both emphysema and airway disease were inversely associated with exercise capacity. Subjects with higher CT emphysema ($r = -0.53, p < 0.0001$, Fig. 1) or WA% of the 6th generation of RB1 ($r = -0.28, p = 0.009$, Fig. 2) walked significantly less in 6 min. There was not a significant correlation between 6-MWD and WA% of the 3rd to the 5th generation airways (Table 3). Subjects with higher CT emphysema had lower BMI ($r = -0.25, p = 0.015$) and FEV$_1$%P ($r = -0.68, p < 0.0001$), and higher degree of hyperinflation estimated by RV/TLC%P ($r = 0.56, p < 0.0001$). Subjects with greater WA% of the 4th ($r = -0.23, p = 0.03$), 5th ($r = -0.22, p = 0.04$), and 6th generation ($r = -0.39, p = 0.0002$) of RB1 also had lower FEV$_1$%P.

CT emphysema but not airway disease remained significantly associated with exercise capacity in the multivariate analysis adjusted for age, gender, BMI, RV/TLC%P, scanner

| Table 1 | Anthropometric, lung function, exercise capacity, CT assessment, and procedure data for the 93 subjects. |
| Variable$^a$ | Mean $\pm$ (SD)$^a$ |
| Age (years) | 66.7 $\pm$ 8.8 |
| Female Gender (n, %) | 40 (43) |
| Body Mass Index (kg/m$^2$) | 26.2 $\pm$ 4.7 |
| Smoking History (pack years) | 54.2 $\pm$ 31.7 |
| FEV$_1$ (%predicted) | 57.1 $\pm$ 24.3 |
| FVC (%predicted) | 81.6 $\pm$ 19.3 |
| FEV$_1$/FVC ratio | 0.5 $\pm$ 0.2 |
| RV (%predicted) | 159.4 $\pm$ 57.9 |
| TLC (%predicted) | 111.9 $\pm$ 18.9 |
| RV/TLC ratio (%predicted) | 131.6 $\pm$ 32.3 |
| 6-Minute Walk Distance (m) | 331.2 $\pm$ 149.4 |
| SpO$_2$ at the end of 6MWD (%) | 91.7 $\pm$ 6.5 |
| %LAA-950 (%) | 16.8 (9.0–32.6) |
| WA% of 3rd generation of RB1 (%) | 60.5 $\pm$ 6.2 |
| WA% of 4th generation of RB1 (%) | 66.4 $\pm$ 7.7 |
| WA% of 5th generation of RB1 (%) | 72.3 $\pm$ 7.5 |
| WA% of 6th generation of RB1 (%) | 78.8 $\pm$ 6.5 |
| Type of procedure (n, %) | Wedge resection or Lobectomy 57 (61) |
| Lung Volume Reduction Surgery 11 (12) |
| Lung Transplant 10 (11) |
| Surgical Lung Biopsy 5 (5) |
| No Tissue Obtained 10 (11) |

$^a$ Values are expressed as mean $\pm$ standard deviation, except for female gender and type of procedure (n, %), and %LAA-950 median (interquartile range).
Values are expressed as mean and for TLC%P, predictors (for RV/TLC%P, a single-variable model containing lung volume measures as

Discussion

In this study we observed that in univariate analysis whole lung emphysema percentage assessed by volumetric CT and airway wall thickening of only the 6th generation airway of right upper lobe apical segment correlated with the distance walked in 6 min in subjects with COPD. Multivariate analysis showed that in this cohort emphysema but not airway disease contributed independently to exercise capacity as assessed by 6MWD.

The %LAA-950 is inversely associated with 6MWD suggesting that emphysema has a deleterious impact on exercise capacity. Previous studies examining the relationship between objective and semi-objective measures of emphysema and exercise capacity have yielded conflicting results. An early study found that CT emphysema correlated with 12-min walk distance20 and Lee et al21 found that %LAA-950 obtained from volumetric CT scans is inversely correlated with 6MWD (r = −0.53). In contrast to these, Taguchi et al33 found that using a subjective visual assessment of emphysema in 32 subjects with COPD there was no relationship between their measures of emphysema and 6MWD. Technique differences and their smaller sample size may explain the disparity with our results. In another recent study, Mair et al34 did not find a correlation between %LAA-950 and 6MWD. A lower median (5.5%) and a narrower interquantile range of CT emphysema percentage (1.6–17.5%) of their subjects may partly explain the disparity with the present result.

Airway wall thickening of the most distal airway assessed in this study was inversely related to 6MWD in univariate analysis. A previous cited study failed to find such a relationship.21 One reason for this discrepancy is that in the Lee study only segmental bronchi were assessed. Our finding suggests that airway wall thickening of a more distal airway assessed by CT scanning is associated with changes in 6MWD. A partial explanation for the relationship between WA% and 6MWD is that the airway wall thickening in COPD may explain the disparity with our results. In another recent study, Mair et al34 did not find a correlation between %LAA-950 and 6MWD. A lower median (5.5%) and a narrower interquantile range of CT emphysema percentage (1.6–17.5%) of their subjects may partly explain the disparity with the present result.

Figure 1 Scatter plot of 6-min walk distance to emphysema assessed by CT defined as percentage of low attenuation areas below −950 Hounsfield Units (%LAA-950) in subjects with COPD.
length is correlated with better exercise performance after addition, Lando et al. showed that a change in diaphragm occupation by emphysematous lesions in the whole lung could in turn lead to a reduction of the subject's exercise airflow limitation and gas trapping destruction of the lung more than airway remodeling of the disease may be responsible for the effect on the reduction of exercise capacity through the lungs. This may not be appropriate as it has been shown that there are variations in airway dimensions and in correlations between %LAA and exercise capacity in subjects with COPD.

Second, the LTRC is a multicenter initiative employing different brands and generations of CT scanners. Despite efforts to standardize image acquisition and reconstruction, there were likely systematic differences in CT scans introducing bias in our results. However, present results on the correlations of %LAA-950 with FEV1%P and BMI and of airway wall thickness of 3rd to 6th generations of RB1 with FEV1%P are consistent with previous studies and are supportive of our findings regarding the relation of CT indexes to 6MWD.

Finally, we assumed that WA% of 3rd to 6th generations of RB1 may represent the airway dimensions of the rest of the lungs. This may not be appropriate as it has been shown that there are variations in airway dimensions and in correlations between WA% and FEV1%P in the right upper and right lower lobes. Further studies are needed to assess whether or not there is variability in correlations between WA% and exercise capacity through the lungs.

In summary, the present study suggests that airway wall thickening of a distal airway generation and emphysema assessed by CT correlates with 6-min walk distance in subjects with COPD, but only emphysema seems to contribute independently to exercise capacity. As this was

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**Table 3** Pearson's correlation coefficients (r) between 6-min walk distance, lung function, emphysema and airway disease assessed by CT for the 93 subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Six-minute walk distance (m)</th>
<th>r Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (%predicted)</td>
<td>0.48</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>FVC (%predicted)</td>
<td>0.32</td>
<td>0.002</td>
<td></td>
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<tr>
<td>FEV/FVC ratio</td>
<td>0.47</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>RV (%predicted)</td>
<td>-0.40</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>TLC (%predicted)</td>
<td>-0.22</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>RV/TLC ratio (%predicted)</td>
<td>-0.39</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>%LAA-950 (%)</td>
<td>-0.53</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>WA% of 3rd generation of RB1 (%)</td>
<td>0.12</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>WA% of 4th generation of RB1 (%)</td>
<td>-0.18</td>
<td>0.09</td>
<td></td>
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<tr>
<td>WA% of 5th generation of RB1 (%)</td>
<td>-0.10</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>WA% of 6th generation of RB1 (%)</td>
<td>-0.28</td>
<td>0.009</td>
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</tr>
</tbody>
</table>

%LAA-950, Percentage of Low Attenuation Areas Below -950 Hounsfield Units; WA%, Wall Area Percentage; RB1, Apical Bronchus of the Right Upper Lobe.
a retrospective analysis and the population study may not be representative of the normal COPD population, further prospective studies involving large study cohort are needed to assess the observed relationship between CT indexes and exercise capacity.

Conflicts of interest

There no conflicts of interest for all the authors except for EKS. Edwin K. Silverman received an honorarium for a talk on COPD genetics in 2006, and grant support and consulting fees from GlaxoSmithKline for two studies of COPD genetics. EKS received an honorarium from Bayer for a symposium at the ERS Meeting in 2005. EKS received honoraria in 2007 and 2008 and consulting fees from AstraZeneca.

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References


