Relative contributions of emphysema and airway remodelling to airflow limitation in COPD: Consistent results from two cohorts

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ABSTRACT

Background and objective: The relative contributions of emphysema and airway remodelling to airflow limitation remain unclear in chronic obstructive pulmonary disease (COPD). We aimed to evaluate the relative contributions of emphysema and airway wall thickness measured by quantitative computed tomography (CT) to the prediction of airflow limitation in two separate COPD cohorts.

Methods: Pulmonary function tests and whole-lung CT were performed in 250 male smokers with COPD, including 167 from University Medical Center at Ho Chi Minh City, Vietnam, and 83 from Shiga University of Medical Science Hospital, Japan. The same CT analysis software was used to measure the percentage of low attenuation volume (%LAV) at the threshold of −950 Hounsfield units and the square root of wall area of a hypothetical airway with an internal perimeter of 10 mm (Pi10). The standardized coefficients in multiple linear regressions were used to evaluate the relative contributions of %LAV and Pi10 to predictions of FEV1/FVC and FEV1% predicted.

Results: Both %LAV and Pi10 independently predicted either forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) or FEV1% predicted (P ≤ 0.001 for all standardized coefficients). However, the absolute values of the standardized coefficients were 2–3 times higher for %LAV than for Pi10 in all prediction models. The results were consistent in the two COPD cohorts.

Conclusions: %LAV predicts both FEV1/FVC and FEV1 better than Pi10 in patients with COPD. Thus, emphysema may make a greater contribution to airflow limitation than airway remodelling in COPD.

Key words: airway remodelling, chronic obstructive pulmonary disease, computed tomography, emphysema, quantitative imaging.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation, which is demonstrated by a post-bronchodilator FEV1/FVC (ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC)) less than 70%.1 The airflow limitation mainly results from obstruction of small airways,2,3 which is the consequence of small airway obliteration due to narrowing and loss of terminal bronchioles,4 airway wall thickening due to airway remodelling and loss of lung elastic recoil due to
emphysematous lung destruction. However, the relative contributions of emphysema and airway remodelling to airflow limitation in COPD remain unclear.

To fully evaluate morphological changes in patients with COPD, lung specimens are needed. Unfortunately, lung biopsy is not a feasible option for most patients who participate in cross-sectional or longitudinal studies. To overcome this obstacle, investigators have used non-invasive modalities including quantitative computed tomography (CT) to indirectly examine those changes. The extent of emphysema measured by using quantitative CT correlates with that measured macroscopically or microscopically or with indices of airflow limitation such as FEV1/FVC and FEV1. Airway wall thickness of relative large can also be used to predict that of small conducting airways. Furthermore, CT-based emphysema and airway wall thickness independently predict FEV1 in COPD. However, little is known about which one makes a greater contribution to that prediction. This study was conducted to evaluate the relative contributions of emphysema and airway wall thickness, measured by using three-dimensional CT analysis software, to the prediction of airflow limitation in two separate COPD cohorts. Some results of this study have been previously reported as an abstract.

METHODS

Study design
This is a cross-sectional study in two ongoing COPD cohorts. One recruited COPD patients from the Outpatient Clinic of University Medical Center at Ho Chi Minh City, Vietnam (HCMC cohort), from June 2011 to June 2013. Another recruited COPD patients from the Outpatient Clinic of Shiga University of Medical Science Hospital, Japan (SUMS cohort), from June 2012 to June 2013. Each recruited patient underwent a complete medical interview, physical examination, pulmonary function tests and whole-lung CT on the same day. This study was conducted in accordance with the amended Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating institution. Written informed consent was obtained from all patients.

Study patients
Patients were recruited if they met all of the following criteria: age between 40 and 85 years, former or current cigarette smokers with more than 10 pack-years and definitive diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines. Patients were excluded for any of the following reasons: female (COPD is rare in women in both cohorts), a history of asthma, COPD exacerbations within 6 weeks, chronic respiratory failure, and abnormalities on plain chest X-ray other than emphysema and/or minor linear opacities.

Pulmonary function tests
In the HCMC cohort, all patients underwent spirometry and measurement of diffusing capacity of the lung for carbon monoxide (DLCO) following American Thoracic Society/European Respiratory Society recommendations, as described elsewhere. Because the spirometric reference values for the Vietnamese are not currently available, all post-bronchodilator parameters except FEV1/FVC are presented as percentages of the predicted values based on the NHANES III equations with a correction factor of 0.88.

In the SUMS cohort, all patients underwent spirometry and measurement of DLCO using FUDAC-77 (Fukuda Densihi, Tokyo, Japan) before and after inhaling 20 μg proclaterol. All manoeuvres met Japanese Respiratory Society standards. Post-bronchodilator parameters except FEV1/FVC are presented as percentages of the predicted values based on the Japanese reference equations.

Quantitative CT analysis
In the HCMC cohort, all patients were scanned by using the same 64-slice CT scanner, Toshiba Aquilion 64 (Toshiba Corp., Tokyo, Japan), as previously reported.

In the SUMS cohort, all patients were scanned by using the same 320-slice CT scanner, Toshiba Aquilion ONE. The CT scanning protocol was non-contrast, spiral mode, pitch of 0.906, 120 kVp, 210 mA, rotation time of 0.5 s, collimation of 0.5 mm, at suspended full inspiration, from apex to bottom of the lungs. CT images were reconstructed with 1-mm slice thickness, 0.5-mm interval, 350-mm field of view, 512 × 512 matrix and FC03 kernel.

All CT images of the two cohorts were analysed by using Apollo 1.2 software (VIDA diagnostics, Coralville, IA, USA; http://www.vidadiagnostics.com) at a laboratory of the SUMS.

The extent of emphysema was measured by density mask and percentile point methods. For the density mask method, emphysema was defined as the percentage of lung volume with CT attenuation value below −950 Hounsfield units (HU)—known as percentage of low attenuation volume (%LAV) at the threshold of −950 HU (Supplementary Fig. S1a). For the percentile point method, emphysema was defined as the lowest 15th percentile point (PD15) at which 15% of lung density is distributed below it on the histogram of the whole lungs.

All visible airways in both lungs up to the fifth generation—subsubsegmental bronchi—were segmented and measured (Supplementary Fig. S1b,c). Because the software has been validated on physical phantoms with internal perimeter >6 mm2 and the majority of bronchial segments with the third generation have internal perimeter <20 mm, only bronchial segments with internal diameters from 6 to 20 mm were selected for estimating the square root of wall area of a hypothetical airway with an internal perimeter of 10 mm (P10)—a standardized index of airway wall thickness. P10 is calculated from the linear regression in which the square root of wall area of each measured segment is plotted against its internal perimeter (Supplementary Fig. S1d).

Patients with noisy CT images or lung abnormalities other than emphysema were excluded from the
The statistical analysis was done by using IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA). More details about the statistical analysis are provided in Supplementary Appendix S1.

**RESULTS**

**Study patients**
Among patients recruited, 167 in the HCMC cohort and 83 in the SUMS cohort were included in the statistical analysis. In the HCMC cohort, 30 out of 197 (15.2%) patients were excluded from the statistical analysis; the most common reason was noisy CT images (Supplementary Table S1). Patients in the HCMC cohort were younger and shorter, smoked less and had a lower total lung capacity (TLC) than those in the SUMS cohort (Table 1). The mean FEV1% predicted and mean DLCO% predicted were lower in the HCMC than in the SUMS cohort. However, the mean FEV1/FVC was not different between the two cohorts.

**Univariate analysis of CT measures**
The extent of emphysema measured as %LAV or PD15 was less severe, but the airway wall thickness measured as Pi10 was thicker in the HCMC than in the SUMS cohort (Table 2).
Relative contributions of CT measures

Using standard multiple regressions, both %LAV and Pi10 independently predicted either FEV₁/FVC (Table 4) or FEV₁% predicted (Table 5) in both COPD cohorts. However, %LAV predicted both FEV₁/FVC and FEV₁ better than Pi10, as indicated by higher absolute values of the standardized coefficients or higher semipartial coefficients for %LAV than for Pi10. In the HCMC cohort, FEV₁/FVC declined 2.8 times greater for each SD increase in log(%LAV) (by 0.65 SD) than in Pi10 (by only 0.23 SD); the total variability of FEV₁/FVC was explained 40.6% by log(%LAV), but only 5.1% by Pi10 (Table 4). In the SUMS cohort, FEV₁/FVC declined 2.7 times greater for each SD increase in %LAV (by 0.73 SD) than in Pi10 (by only 0.27 SD); the total variability of FEV₁/FVC was explained 51.6% by %LAV, but only 6.9% by Pi10. Similarly, in the HCMC cohort, FEV₁% predicted declined 2.1 times greater for each SD increase in log(%LAV) than in Pi10; the total variability of FEV₁% predicted was explained 23.2% by log(%LAV), but only 6.6% by Pi10 (Table 5). In the SUMS cohort, FEV₁% predicted declined 1.9 times greater for each SD increase in %LAV than in Pi10; the total variability of FEV₁% predicted was explained 34.1% by %LAV, but only 13.4% by Pi10.

When %LAV was replaced with PD15 as an index of emphysema, the results were repeatable for both FEV₁/FVC (Supplementary Table S2) and FEV₁% predicted (Supplementary Table S3), except that PD15 was positively correlated with indices of airflow limitation.

**DISCUSSION**

Results of this study show that both %LAV and Pi10 independently predicted either FEV₁/FVC or FEV₁,
predicted. However, %LAV predicted both FEV1/FVC and FEV1 better than Pi10. The results were consistent in two separate COPD cohorts, which differed by ethnicity, mean age, mean FEV1, % predicted and mean CT measures.

The finding that both %LAV and Pi10 were independent predictors of FEV1,% predicted is consistent with findings from previous studies, which used two-dimensional CT analysis software to measure the same CT measures.\(^{16,19}\) However, the present study

**Table 4** Relative contributions of CT measures to predictions of FEV1/FVC by standard multiple regressions\(^1\)

<table>
<thead>
<tr>
<th>Parameters of prediction model</th>
<th>HCMC cohort (n = 167)</th>
<th>SUMS cohort (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstandardized coefficient (95% CI)</td>
<td>%LAV</td>
<td>Pi10</td>
</tr>
<tr>
<td>Unstandardized coefficient</td>
<td>-9.95 (−11.79, −8.12)</td>
<td>-19.4 (−29.5, −9.3)</td>
</tr>
<tr>
<td>Standardized coefficient</td>
<td>-0.65</td>
<td>-0.23</td>
</tr>
<tr>
<td>Semi-partial coefficient</td>
<td>0.406</td>
<td>0.051</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\)The adjusted R\(^2\) was 0.412 for the HCMC cohort and 0.534 for the SUMS cohort.

\(^2\)LAV in the HCMC cohort was log-transformed.

\(^3\)The absolute value refers to how many SD FEV1/FVC would decrease per SD increase in the predictor.

\(^4\)The value expresses the unique contribution of the predictor to the total variability of FEV1/FVC.

\(^5\)Significantly different from zero, applied for the three coefficients at the same time.

CI, confidence interval; CT, computed tomography; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCMC, Ho Chi Minh City; %LAV, percentage of low attenuation volume; Pi10, the square root of wall area of a hypothetical airway with an internal perimeter of 10 mm; SD, standard deviation; SUMS, Shiga University of Medical Science.

**Figure 1** Scatterplots of the association between computed tomography (CT) measures and forced expiratory volume in 1 s (FEV1) % predicted in the (a, b) Ho Chi Minh City (HCMC) and (c, d) Shiga University of Medical Science (SUMS) cohorts. %LAV, percentage of low attenuation volume; Pi10, the square root of wall area of a hypothetical airway with an internal perimeter of 10 mm.
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Table 5  Relative contributions of CT measures to predictions of FEV₁,% predicted by standard multiple regressions

<table>
<thead>
<tr>
<th>Parameters of prediction model</th>
<th>HCMC cohort (n = 167)</th>
<th>SUMS cohort (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%LAV‡</td>
<td>Pi10</td>
</tr>
<tr>
<td>Unstandardized coefficient (95% CI)</td>
<td>-13.28 (−17.00, −9.56)</td>
<td>-35.3 (−55.8, −14.8)</td>
</tr>
<tr>
<td>Standardized coefficient†</td>
<td>-0.48</td>
<td>0.23</td>
</tr>
<tr>
<td>Semi-partial coefficient¶</td>
<td>0.232</td>
<td>0.066</td>
</tr>
<tr>
<td>P value‡†</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
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</table>

The adjusted R² was 0.241 for the HCMC cohort and 0.369 for the SUMS cohort.

The value expresses the unique contribution of the predictor to the total variability of FEV₁,% predicted.

The absolute value refers to how many SD FEV₁,% predicted would decrease per SD increase in the predictor.

The novel finding of the present study is that %LAV predicted both FEV₁/FVC and FEV₁ better than Pi10 in COPD. This finding is consistent in the two separate COPD cohorts and supported by both univariate and multivariate analyses. This helps clarify the finding from a previous study that %LAV had a greater influence than Pi10 on BODE index, which includes FEV₁,% predicted. The finding that %LAV predicted FEV₁/FVC better than Pi10 is in agreement with that of a recent study by Mohamed Hoesein et al., but not the finding that Pi10 predicted FEV₁ better than %LAV. The discrepancy may result from the fact that FEV₁ is presented as post-bronchodilator value in the present study but as pre-bronchodilator value in the Mohamed Hoesein et al.'s study and that all male smokers in the present study have COPD while most male smokers in that study do not have COPD, and thus, their %LAV is insignificant.

There are several possible explanations for why %LAV predicted both FEV₁/FVC and FEV₁ better than Pi10 in COPD. First, %LAV reflects emphysematous lesions, which result in loss of lung elastic recoil. In this instance, the loss of lung elastic recoil may be a stronger determinant of airflow limitation than airway wall thickening. Second, Pi10 only reflects small airway wall thickening, which is one component of small airway obstruction. There is evidence that small airway obstruction in COPD also results from complete obliteration of small airways as well as the accumulation of inflammatory mucous exudates within the lumen. Neither of these is captured by Pi10. Finally, airway wall may not be thickened in all COPD patients.

Results of the present study suggest that emphysema may make a greater contribution to airflow limitation in COPD than airway remodelling. This implication has been corroborated in some longitudinal studies, which have showed that %LAV plays a greater role as a biomarker than Pi10. A greater extent of emphysema on baseline CT is associated with a greater decline in FEV₁ in smokers or in subjects with established COPD. In addition, %LAV has been shown to predict respiratory-related mortality and all-cause mortality in COPD while Pi10 has not. This implication also means that interventions targeting emphysema may result in better outcomes than those targeting airway remodelling in patients with COPD.

Because the results were consistent in two COPD cohorts with different baseline characteristics and CT scanning protocols, the results may be generalized to other Asian COPD populations. The fact that Vietnamese patients have smaller lungs (lower TLC) makes their FEV₁,% predicted worse than Japanese patients, even though FEV₁/FVC was similar. The differences in age, pack-years of smoking and CT scanning protocol may make %LAV lower in the HCMC than in the SUMS cohort. The threshold of −950 HU to define emphysema may underestimate %LAV in the Vietnamese, whereas it may not in the Japanese. Nevertheless, the results in this study are robust because %LAVs generated by different thresholds are certainly correlated with each other. In addition, when replacing %LAV with PD15, the results were repeatable in both cohorts.

This study has some limitations. First, the sample size of each cohort is relatively small. The associations in Table 3 could be strengthened if the sample size of each cohort was larger. Second, %LAV and Pi10 explained only 24–53% of the total variability of airflow limitation. It is likely that these CT measures are indirect and incomplete indices of the structural and functional changes that contribute to airflow limitation in COPD. The adjusted R² in Tables 4 and 5 could be greater if an index of air trapping assessed by inspiratory/expiratory CT scans, which is also associated with airflow limitation, is added to the prediction models. Finally, Pi10 reflects the wall thickness of airways with an internal diameter of 2 mm that are the main site of airway obstruction in COPD.
However, Pi10 has been shown to be related with airway thickening of small airways evaluated by histology.17 In conclusion, %LAV predicted both FEV1/FVC and FEV1 better than Pi10 in patients with COPD. Thus, emphysema may make a greater contribution to airflow limitation than airway remodelling in COPD.

Acknowledgements

The study was partially funded by JSPS KAKENHI Grant No. 18590847. The authors would like to thank the staff of the Respiratory Care Center, University Medical Center at Ho Chi Minh City, Vietnam, for recruiting the patients. The authors also want to thank Prof. Peter D. Paré, MD, James Hogg Research Center, University of British Columbia, Vancouver, Canada, for helpful comments on the manuscript.

REFERENCES


Supplementary Information

Additional Supplementary Information can be accessed via the html version of this article at the publisher’s web-site:

Supplementary Figure S1 Measurement of emphysema and airway wall thickness using Apollo 1.2 software.

Supplementary Table S1 Reasons for 30 patients in the Ho Chi Minh City cohort excluded from the study after undergoing CT scans.

Supplementary Table S2 Relative contributions of PD15 and Pi10 to predictions of FEV1/FVC by standard multiple regressions.

Supplementary Table S3 Relative contributions of PD15 and Pi10 to predictions of FEV1% predicted by standard multiple regressions.

Supplementary Appendix S1 More details about computed tomography evaluation and statistical analysis.