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Original Article

Contributors of the Severity of Airflow Limitation in COPD Patients

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Background: Although airway obstruction in chronic obstructive pulmonary disease (COPD) is due to pathologic processes in both the airways and the lung parenchyma, the contribution of these processes, as well as other factors, have not yet been evaluated quantitatively. We therefore quantitatively evaluated the factors contributing to airflow limitation in patients with COPD.

Methods: The 213 COPD patients were aged >45 years, had smoked >10 pack-years of cigarettes, and had a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.7. All patients were evaluated by medical interviews, physical examination, spirometry, bronchodilator reversibility tests, lung volume, and 6-minute walk tests. In addition, volumetric computed tomography (CT) was performed to evaluate airway wall thickness, emphysema severity, and mean lung density ratio at full expiration and inspiration. Multiple linear regression analysis was performed to identify the variables independently associated with FEV_1 - the index of the severity of airflow limitation.

Results: Multiple linear regression analysis showed that CT measurements of mean lung density ratio (standardized coefficient $\beta=-0.46$; $p<0.001$), emphysema severity (volume fraction of the lung less than −950 HU at full inspiration; $\beta=-0.24$; $p<0.001$), and airway wall thickness (mean wall area %; $\beta=-0.19$, $p=0.001$), as well as current smoking status ($\beta=-0.14$; $p=0.009$) were independent contributors to FEV_1.

Conclusion: Mean lung density ratio, emphysema severity, and airway wall thickness evaluated by volumetric CT and smoking status could independently contribute to the severity of airflow limitation in patients with COPD.

Key Words: Pulmonary Disease, Chronic Obstructive; Forced Expiratory Volumes; Tomography, X-Ray Computed

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation with poor reversibility and progression[1]. This airflow limitation is due to pathologic processes in both the airways and lung parenchyma[2]. The relative proportion of these two processes can vary considerably between individuals with the same degree of airflow limitation[3].

Recent advances in multi-channel computed tomography (CT) scanning has allowed the quantitative assessment of both the airway and parenchymal processes. CT measurements of the extent of emphysema, airway thickening, and air trapping, as well as exercise capacity and body mass index (BMI) have been found to correlate with the severity of airflow limitation in COPD patients[4-8]. However, the contribution of each factor to the severity of airflow limitation has not yet been evaluated quantitatively. We therefore evaluated factors contributing the severity of airflow limitation in COPD patients quantitatively.

Materials and Methods

1. Subjects

The 213 COPD patients aged >45 years, who had smoked >10 pack-years of cigarettes, and had a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.7, but did not have bronchiectasis or sequelae of pulmonary tuberculosis were analyzed in this study.

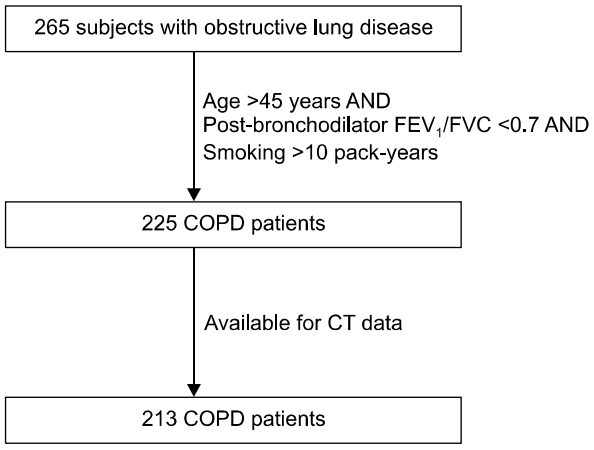

Figure 1. Selection of the study subjects from all subjects with obstructive lung disease. COPD: chronic obstructive pulmonary disease; CT: computed tomography.

The 213 patients were selected from a group of patients with obstructive lung disease (OLD), including those with COPD, asthma and overlap syndrome (Figure 1). The 265 stable patients with OLD were recruited from the pulmonary clinics of 11 hospitals in South Korea from June 2005 to October 2008. The inclusion criteria for patients with OLD have been described elsewhere[9].

All patients were evaluated by medical interviews, physical examinations, spirometry, bronchodilator reversibility tests, and lung volume and six-minute walk tests. In addition, volumetric CT was performed to evaluate airway wall thickness, emphysema severity, and mean lung density ratio at full expiration and inspiration. Multiple linear regression analysis was performed to identify the variables independently associated with FEV_1, the index of the severity of airflow limitation.

Our Institutional Review Board approved analyses of the clinical and imaging data. Individual informed written consent was obtained from all patients.

2. Pulmonary function tests

Spirometry was performed using a Vmax 22 (SensorMedics, Yorba Linda, CA, USA) or a PFDX (MedGraphics, St Paul, MN, USA). To assess post-bronchodilator FEV_1 increases, spirometry was performed pre-bronchodilation and 15 minutes after inhalation of four separate doses of salbutamol 100 μg through a metered-dose inhaler (MDI) with a spacer. The post-bronchodilator FEV_1 increase was expressed as the percent of the predicted normal value. Lung volumes, including total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and residual volume (RV), were measured by body plethysmography (V6200, SensorMedics or PFDX). Diffusing capacity for carbon monoxide (D_{LCO}) was measured by the single-breath method using a Vmax229D (Sensor-Medics) or a Masterlab Body (Jaeger AB, Würtsburg, Germany). All pulmonary func-

tion tests were performed as recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS)[10-12].

3. Computed tomography

Volumetric CT scans were performed on all patients using the Somatom Sensation 16 (Siemens Medical Solutions, Forchheim, Germany), GE Lightspeed Ultra (General Electric Healthcare, Milwaukee, WI, USA), and Philips Brilliance 16 (Philips Medical Systems, Best, Netherlands) 16-slice multi-detector CT (MDCT) scanners. Patients were scanned during suspended full inspiration and expiration in the supine position without respiratory gating. Before CT scans, patients were taught how to inhale and exhale and practiced doing so under the guidance of trained nurses. The CT parameters were: 16×0.75 mm collimation, 100 eff. mAs, and 140 kVp for the Somatom Sensation 16; 16×0.625 mm, 300 mAs, 140 kVp, Pitch 0.938, and 0.5 sec/rot for the GE Lightspeed; and 16×0.75 mm, 133 mAs, 140 kVp, Pitch 1, and 0.75 sec/rot for the Philips 16. Acquired data were reconstructed using a standard algorithm with thicknesses of 0.625～0.8 mm and increments of 0.625～0.8 mm. Each CT scanner was calibrated for water using a standard water phantom monthly and after major maintenance, and for air daily. All screening scans were performed within 24 hours after calibration. Image data were stored in the Digital Imaging and Communications in Medicine (DICOM) format. Using in-house software, images of the whole lung were extracted automatically and the attenuation coefficient of each pixel was measured and calculated. The cutoff between normal lung density and a low-attenuation area (LAA) was defined as −950 HU. From the CT data, the volume fraction of the lung less than −950 HU (V_{950}) and the mean lung density (MLD) were calculated automatically. The ratio of MLD on expiration and inspiration was calculated. The airway dimensions, wall area (WA), lumen area (LA) and wall area percent (WA%; ie, WA/(WA+LA)×100), were measured near the origin of two segmental bronchus (the right apical and left apico-posterior) selected by a consensus reading of two radiologists. The software automatically detects the airway lumen and the inner and outer boundaries of the airway wall using a full-width-half-maximum (FWHM) method[13]. The mean value of each segmental bronchus was used for analysis[8].

4. Statistical analysis

To investigate contributors associated with airflow limitation, FEV_1 was used as the dependent variable in univariate and multivariate analyses. Selected independent variables were BMI, six-minute walk distance (6MWD), smoking status (current or ex-smokers, smoking pack-years), the pulmonary function parameters TLC, FRC, RV/TLC, and D_{Lco} and the CT measurements inspiratory V_{950}, WA%, and MLD ratio. Multiple linear regression analysis was performed to identify which variables were independently associated with FEV_1. All statistical analyses were performed using the SPSS statistical package (SPSS version 12.0, SPSS Inc, Chicago, IL) and p-values <0.05 were considered significant.

Results

Of the 213 patients, 205 (96.2%) were men. Mean patient age was 66.3±7.3 years, mean smoking history was 46.5±25.5 pack-years, and mean FEV_1 was 47.6±15.7% predicted (Tables 1, 2).

Multiple linear regression analysis showed that a significant regression model for FEV_1 comprised volumetric CT measurements of MLD ratio (standardized coefficient $\beta=-0.46$; $p<0.001$), inspiratory V_{950} (%, standardized coefficient $\beta=-0.24$; $p<0.001$), WA% (standardized coefficient $\beta=-0.19$; $p=0.001$) and current smoking status (standardized coefficient $\beta=-0.14$; $p=0.009$) (Table 3). The model did not include BMI, total lung capacity, 6 MWD, or the other variables analyzed ($p\geq0.10$).

Multiple linear regression analysis showed that adjusted r^2 was 0.381 for volumetric CT measurements of MLD ratio, inspiratory V_{950} and WA%. And it showed 0.398 for CT measurements and current smoking status (Table 4).

Table 1. Characteristics of subjects

	Mean	Standard deviation
Age, yr	66.3	7.3
Female/Male	8/205	
Body mass index, kg/m^2	23.0	3.6
Smoking amount, py	46.5	25.5
Smoking history, current/past	73/140	
MMRC scale, 0/1/2/3/4	31/69/69/34/10	
Total score on SGRQ	35.3	18.5
6-minute walk distance, m	432	97
Pulmonary function		
Pre-bronchodilator FEV_1, % of predicted	47.6	15.7
Pre-bronchodilator FVC, % of predicted	71.9	20.6
Pre-bronchodilator FEV_1/FVC, %	45.0	11.0
Post-bronchodilator FEV_1, % of predicted	53.4	16.5
Post-bronchodilator FVC, % of predicted	79.2	20.9
Post-bronchodilator FEV_1/FVC, %	46.5	10.9
FEV_1 increase after salbutamol inhalation, % of predicted normal value	5.8	4.8
TLC, % of predicted	120.6	21.7
VC, % of predicted	94.2	21.6
FRC, % of predicted	135.5	34.1
RV, % of predicted	134.7	51.4
IC/TLC, %	31.7	9.2
D_{Lco}, % of predicted	74.0	28.4

Py: pack year; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; IC: inspiratory capacity; TLC: total lung capacity; VC: vital capacity; FRC: functional residual capacity; RV: residual volume; D_{Lco}: diffusion capacity for carbon monoxide; MMRC scale: modified medical research council dyspnea scale; SGRQ: St George's respiratory questionnaire.

Table 2. Volumetric CT data in 213 patients with COPD

Volumetric computed tomography	Mean	Standard deviation
Inspiratory V_{950}, %*	24.5	15.7
Inspiratory mean lung density	−888.6	23.1
Expiratory V_{950}, %*	14.4	14.4
Expiratory mean lung density	−841.2	41.8
Mean lung density ratio†	0.947	0.034
Wall area, %*,‡	66.1	4.8

*Volume fraction of the lung below −950 HU. †Mean lung density ratio at full expiration and inspiration. ‡Wall area/(wall area +lumen area)×100.

Discussion

We have shown here that mean lung density ratio, inspiratory V_{950}, and wall area %, as evaluated by volumetric CT, as well as current smoking status were significant contributors of FEV_1 in COPD patients. This finding indicates that the severity of airflow limitation could be, in part, determined by imaging measurements of the airway and emphysema.

Structural changes, as assessed by CT scanning, have been reported to correlate with the severity of airflow limitation[7,14-16]. In these previous reports, the structural changes included extent of emphysema, as evaluated by low attenuation area (equivalent to V_{950} in this study), and abnormalities of large airway walls, as evaluated by wall thickness (equivalent to wall area % in this study). In addition, comparison of CT scans at expiration and inspiration was reported to reflect small airway diseases[17,18]. To assess the extent of small airway disease in 34 COPD patients, we developed a CT air-trapping index (mean lung density ratio) by comparing the mean lung density seen on CT scans at full expiration and inspiration[8]. The results presented here also show that mean lung density ratio is the most significant contrib-

Table 3. Multiple stepwise linear regression model for the severity of airflow obstruction (FEV_1)

Variable	Nonstandardized coefficient	Standardized coefficient	p-value
Mean lung density ratio*	−211.76	−0.46	<0.001
Inspiratory V_{950}, %†	−0.24	−0.24	<0.001
Wall area, %‡	−0.60	−0.19	0.001
Current smoking status	−4.68	−0.14	0.009

*Mean lung density ratio of full expiration and inspiration. †Volume fraction of the lung less than −950 HU. ‡Mean wall area, wall area/(wall area+lumen area)×100.

Table 4. Models for studying factors contributing to the severity of airflow obstruction (FEV_1), as determined by multiple linear regression

Variables in the 5 different models	Adjusted r^2
Mean lung density ratio*, Inspiratory V_{950} (%)†, Wall area (%)‡	0.381
Mean lung density ratio, Inspiratory V_{950} (%), Wall area (%), current smoking status	0.398

*Mean lung density ratio at full expiration and inspiration. †Volume fraction of the lung below −950 HU. ‡Wall area (%), wall area/(wall area+lumen area)×100.

utor of the severity of airflow limitation in these patients. This finding is consistent with results showing the importance of small airway disease in the pathogenesis of COPD[6,19]. Although obstruction of the smaller airways has been found to correlate with the severity of airflow limitation[7], to date there have been no accurate CT-based measurements of small airway lesions in COPD patients. We have previously shown that mean lung density ratio correlated with the physiologic air-trapping index (vital capacity−FVC) and FEV_1[8]. The results presented here validate the importance of mean lung density ratio, although it has not yet been confirmed as directly reflecting small airway disease.

Emphysema severity and airway wall thickness, as determined by CT scans, have also been found to correlate with FEV_1[20-23]. Our findings confirm these results, in that we found that emphysema severity and large airway wall thickness, as measured by CT scan, could contribute airflow limitation. Cigarette smoking, the major risk factor for COPD, causes abnormalities by inducing inflammation in the lung parenchyma and airways. Indeed, we found that current smoking status was an independent contributor of FEV_1 in COPD patients, whereas smoking history, as assessed by pack-years, was not. Although the amount of previous smoking is related to the severity of COPD, it may not be an independent predictor of FEV_1 after correction for the morphologic changes of the airway and emphysema that are thought to result from smoking.

Our multiple linear regression analysis did not include BMI, total lung capacity or 6 MWD, indicating that the contributions of these factors to FEV_1 may not be independent but may be indirectly influenced by the morphologic changes measured by CT scans.

Although we evaluated FEV_1 as the dependent variable for contributing the severity of airflow limitation, it has been suggested that the severity of airflow limitation be evaluated by post-bronchodilator FEV_1 in COPD patients[24]. Repeat multiple linear regression analysis using post-bronchodilator FEV_1 as the dependent variable resulted in a similar regression model, with mean lung density ratio (standardized coefficient $\beta=-0.44$; $p<0.001$), inspiratory V_{950} (%, standardized coefficient $\beta=-0.30$; $p<0.001$), wall area% (standardized coefficient $\beta=-0.16$; $p=0.003$) and current smoking status (standardized coefficient $\beta=-0.15$; $p=0.006$) being independent contributors of post-bronchodilator FEV_1.

This study had several limitations. First, the mean

lung ratio measured by volumetric CT may not completely reflect small airway disease. We have not shown a direct correlation between mean lung ratio and the severity of small airway disease in COPD patients. A direct correlation needs to be assessed by the pathologic or pathophysiologic evaluation of small airway disease, in accordance with changes in mean lung density.

Another limitation was that our study subjects were predominantly male smokers, either present or past. The high proportion of males in our study may be due to the high prevalence of male smokers and very low prevalence of female smokers in Korea. As there may be gender differences in COPD[25,26], further investigations are warranted.

In conclusion, we found that mean lung density ratio, emphysema severity, and airway wall thickness, as measured by volumetric CT, as well as smoking status, could contribute the severity of the airflow limitation in patients with COPD.

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