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Quantitative Assessment of Airway Wall Thickening in Combined Pulmonary Fibrosis and Emphysema Patients According to Cumulative Cigarette Smoking

Li YZ[1] and Jin GY[1*]

[1]Department of Radiology, Chonbuk National University Medical School and Hospital, Institute of Medical Science, Research Institute of Clinical Medicine, Biomedical Research Institute of Chonbuk National University South Korea

[*]Corresponding author:

Gong Yong Jin, Department of Radiology, Chonbuk National University Medical School and Hospital, Institute of Medical Science, Research Institute of Clinical Medicine, Biomedical Research Institute of Chonbuk National University Hospital, 634-18 Keumam-Dong, Jeonju, Jeonbuk 561-712 South Korea, E-mail: gyjin@jbnu.ac.kr

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Keywords:

Combined pulmonary fibrosis and emphysema; Airway wall remodeling; Smoking; Tomography

Abbreviations:

CPFE: Combined Pulmonary Fibrosis and Emphysema; PFT: Pulmonary Function Test; DLco: Diffusion Capacity of Lung for Carbon Monoxide; BMI: Body Mass Index; FVC: Forced expiratory Vital Capacity; FEV1; Forced Expiratory Volume in 1 second; FEF25-75%: Forced Expiratory Flow Between 25-75%; TLC: Total Lung Capacity; Pi10: The square root wall area at the inner perimeter of a 10mm diameter airway; MLA; Mean Lung Attenuation; %LAAI-950: Percentage area with CT Attenuation Values Less than -950 HU at Inspiration; ILA: Inner luminal area of segmental bronchi; AWT: Airway Wall Thickness of segmental bronchi; AI: Airway Inner Parameter; WAF: Wall Area Fraction of segmental bronchi (percentage wall area/total bronchial area).

1. Abstract

1.1. Purpose: The aim of this study was to evaluate role of Pi10 as a clinically relevant biomarker of smoking-related airway injury in patients with Combined Pulmonary Fibrosis and Emphysema (CPFE) in CT according to cumulative cigarette smoking.

1.2. Material and Methods: We retrospectively assessed 54 CPFE patients and 18 healthy non-smokers (control) who underwent non-enhanced CT. We quantitatively analyzed airway changes (the inner luminal area, airway inner parameter, airway wall thickness, Pi10, skew, and kurtosis) for CT of CPFE patients according to cumulative cigarette smoking. Airway change data among the three groups of CPFE patients (group I: less than 30 pack years, group II: 30 to 50 pack years, group III: more than 50 pack years) with control group were compared by one-way ANOVA.

1.3. Results: In CPFE group, Pi10 in group I and II were normal. However, group III (more than 50 pack years) had significantly increased Pi10 (mean increase 0.04, P=0.013) and increased airway wall thickness of the segmental bronchi (mean increase 0.06 mm, P=0.005).

1.4. Conclusion: Pi10 could be clinically relevant biomarker of smoking-related airway injury in CPFE patients.

2. Introduction

Combined Pulmonary Fibrosis and Emphysema (CPFE) is reported to occur in approximately 8% of patients with IPF. CPFE is most often observed in males between 65-70 years old and usually

occurs insignificant smoking histories [1, 2]. According to previous research, individuals with CPFE generally have normal or subnormal spirometry results but have severely diminished diffusion capacity of carbon monoxide (DLco) based on pulmonary function tests [1-3]. Objective Quantitative CT (QCT) measurements have become increasingly recognized as an essential method for studying CPFE. While there have been studies investigating the relationship between QCT measurement and pulmonary function tests [4, 5], none of these studies compared the quantitative measurements of airway remodeling and results of pulmonary function tests in CPFE patients. One study from Washko et al. [3] demonstrated that both spirometric restriction and HRCT positively associate with the extent of tobacco exposure in CPFE patients. However, they did not perform quantitative analyses investigating which parameters assessed by pulmonary function tests are affected by pack years and to what extent they are affected.

In this study, we conducted QCT measurements and compared the results with pulmonary function test results in CPFE patients according to cumulative cigarette smoking. We hypothesized that pack years would affect airway remodeling and change of lung density in CPFE patients and that the degree of these alterations would associate with pulmonary function test results.

3. Method

This was a retrospective study approved by our Institutional Review Board. Therefore, informed consent was waived. We obtained medical records and non-enhanced CT images taken from September 2013 to October 2015, which were reviewed by a radiologist. Diagnosis of CPFE is confirmed on the basis of findings on CT [2]. 54 CPFE patients were included in the study. A matching process was used to identify controls in order to reduce confounding effects. Control subjects matched for demographic variables including age (±3 years), year of CT scans and smoking status (nonsmoker) were used as controls. A total of 18 subjects were enrolled as controls.

PFTs were performed according to the American Thoracic Society guidelines [6]. A portable spirometer (Chest Graph HI-701, Chest Co. Ltd, Tokyo, Japan) was used, and the following values were assessed: FEV_1, Forced Vital Capacity (FVC), FEV_1/ FVC ratio and diffusion capacity of lung for carbon monoxide (DLco). All PFTs were performed on the same day as the chest CT scans.

Pack years was used to quantify smoking history, and it was defined as the number of daily cigarette packs (20 cigarettes per pack) smoked multiplied by the years of smoking. Patients were divided into 3 groups based on mean pack years: group I included individuals with less than 30 pack years, group II included individuals with 30 to 50 pack years, and group III included individuals with more than 50 pack years. Non-smoker patients were control.

A multi-detector CT scanner (Somatom Sensation 16, Siemens Medical Solution, Erlangen, Germany, or Somatom Definition FLISH, Siemens Medical Solution, Forchheim, Germany) was used to take the volumetric assessment. The patients were required to hold their breath at deep inspiration in the supine position. The following CT parameters were used: tube current of 200 mAs, tube voltage of 120 kVp, rotation time of 0.5 or 0.33 seconds, reconstructed slice thickness of 1.0 mm, reconstructed slice interval of 0.7 mm, reconstruction kernel of B35f, and acquisition of 16×1or128×0.6mm.

All CT images were quantitatively assessed using Pulmonary Workstation using the APOLLO software (VIDA Diagnostics, Inc., Coralville, IA). The Pi10, also, was calculated as the square root wall area at the inner perimeter of a 10mm diameter airway [7]. The Pi10 value was obtained as a global comparative measure using 6 segmented airway branches. The extent of emphysematous lesions was determined by evaluating the low attenuation area (values lower than -950 Hounsfield, %LAAI-950), the threshold value at 15th percentile (PER15, HU) and mean lung attenuation (MLA%) [8, 9]. Total Lung Capacity (TLCCT) was also calculated based on inspiratory CT images.

All descriptive data are depicted as the mean and Standard Deviation (SD) for the continuous variables. Independent sample t-tests and one-way ANOVA analyses were used to compare normally distributed continuous variables. The Mann-Whitney U test and Kruskal-Wallis test were used for non-normally distributed data. Statistical analyses were performed using SPSS 12.0.1 software. Associations were considered statistically significant at $P<0.05$.

4. Result

The mean of age was 68.56±6.03 years in the control group and 70.51±7.51 years in the CPFE group. The DLco was significantly different between the two groups, with the CPFE group demonstrating a much lower diffusion capacity (72.90±21.48 %) compared to controls (110.00±9.56 %) ($P<0.001$). Additionally, the LAAI-950 was significantly different between the control (0.64±0.58%) and CPFE groups (5.39±6.40%) ($P<0.001$). Mean skew (2.58±0.36) and kurtosis (7.64±2.36) in the control group were significant different in those of the CPFE patients (1.89±0.37 and3.62±1.70, respectively; $P<0.001$). However, the PFT results, with the exception of the DLco and the Pi10 results, were not significantly different between the control and the CPFE groups.

A comparison of QCT and PFT measurements according to pack years are shown in (Table 1). Individuals in the CPFE group were classified into subgroups based on mean pack years (0-29, 30-50, 51+). Of the PFT measurements, only the DLco was significantly different among the three groups and group III, more than 50 pack years, severely decreased DLco (mean, 58.36±11.83 %). Meanwhile, in QCT, mean lung attenuation, kurtosis, and Pi10were significantly different of the QCT measurements among CPFE

groups assessed. The mean Pi10 was 3.97±0.05in the control group,3.96±0.07 in group I,3.96±0.05 in group II, and 4.01±0.05 in group III, group III had significantly increased Pi10 (mean increase 0.04, P=0.013). When compares airway parameters at the segmental level according to pack years, the ILA, AI and WAF results were not significantly different among the three groups. However, the AWT results were significantly different among the three groups by Kruskal Wallis Test (P=0.005). The mean AWT was 1.77±0.11 in the control group, 1.71±0.09 in group I, 1.72±0.08 in group II, and 1.83±0.14 in group III. Evidence of airway remodeling was mostly observed in individuals with more than 50 pack years. Specifically, the Pi10 was significantly increased and DLco was significantly decreased in individuals with more than 50 pack years compared with other groups (P<0.05). (Figure 1A and 1B).

Table 1: Comparison of the Quantitative CT Measurements and Pulmonary Function Tests by Smoking Intensity in CPFE patients.

	Control (n=18)	CPFE patients (n=54)				
		Group I (n=12)	Group II (n=24)	Group III (n=18)	P value	*Post hoc*
FVC (%)	95.89±11.94	93.67±19.21	96.76±12.81	96.46±16.32	0.933	
FEV_1 (%)	105.89±16.61	101.00±25.89	97.74±17.82	102.92±14.87	0.406	
FVE_1/FVC	77.00±5.29	73.33±12.09	70.06±10.86	75.24±6.21	0.08	
$FEF_{25-75\%}$(%)	91.00±26.87	87.92±47.85	70.87±26.75	90.19±34.26	0.139	
DLCO (%)	110.00±9.56	80.45±24.45	77.41±20.69	58.36±11.83	<0.001	I, II III, IV
TLC_{CT}(L)	5146.77±824.47	4972.09±1076.39	5031.03±864.51	4706.35±750.56	0.342	
MLA (HU)	-839.86±15.95	-837.54±25.31	-826.00±28.80	-811.22±25.30	0.004	I II III, IV
LAA_{I-950}(HU)*	0.64±0.58	6.10±5.20	6.55±8.19	3.38±3.60	0.006	I IV, II III
ILA (%)	65.300±11.55	69.17±9.34	65.81±11.50	67.86±12.19	0.828	
AI (mm)	29.23±2.62	30.18±2.32	29.42±2.80	29.99±3.04	0.867	
AWT (mm)	1.77±0.11	1.71±0.09	1.72±0.08	1.83±0.14	0.012	II III, IV
AF (%)	0.49±0.02	0.48±0.02	0.49±0.03	0.50±0.02	0.146	
Skew*	2.58±0.36	1.94±0.54	1.90±0.33	1.82±0.28	0.057	I IV, II III
Kurtosis*	2.58±0.36	4.38±2.03	3.64±1.78	3.09±1.17	0.019	I IV, II III
Pi10(mm)*	3.97±0.05	3.96±0.07	3.96±0.05	4.01±0.05	0.026	I II III, IV

Definition of abbreviations: FVC, Forced expiratory vital capacity; FEV1, Forced expiratory volume in 1 second; FEF25-75%, Forced expiratory flow between 25-75%; DLCO, Diffusion capacity of lung for carbon monoxide; TLC, Total lung capacity; Pi10, inner perimeter of 10 mm; MLA, Mean lung attenuation; %LAAI-950, Percentage area with CT attenuation values less than -950 HU at inspiration;ILA, Inner luminal area of segmental bronchi; AWT, airway wall thickness of segmental bronchi; AI, airway inner parameter; WAF, wall area fraction of segmental bronchi (percentage wall area/ total bronchial area).

Control: non-smoking patients, Group I: smoking intensity less than 30 pack years, Group II: smoking intensity 30 to 50 pack years, Group III: smoking intensity more than 50 pack years

*non-normally distributed data which were used Kruskal Wallis Test

P value: One-way ANOVA analysis

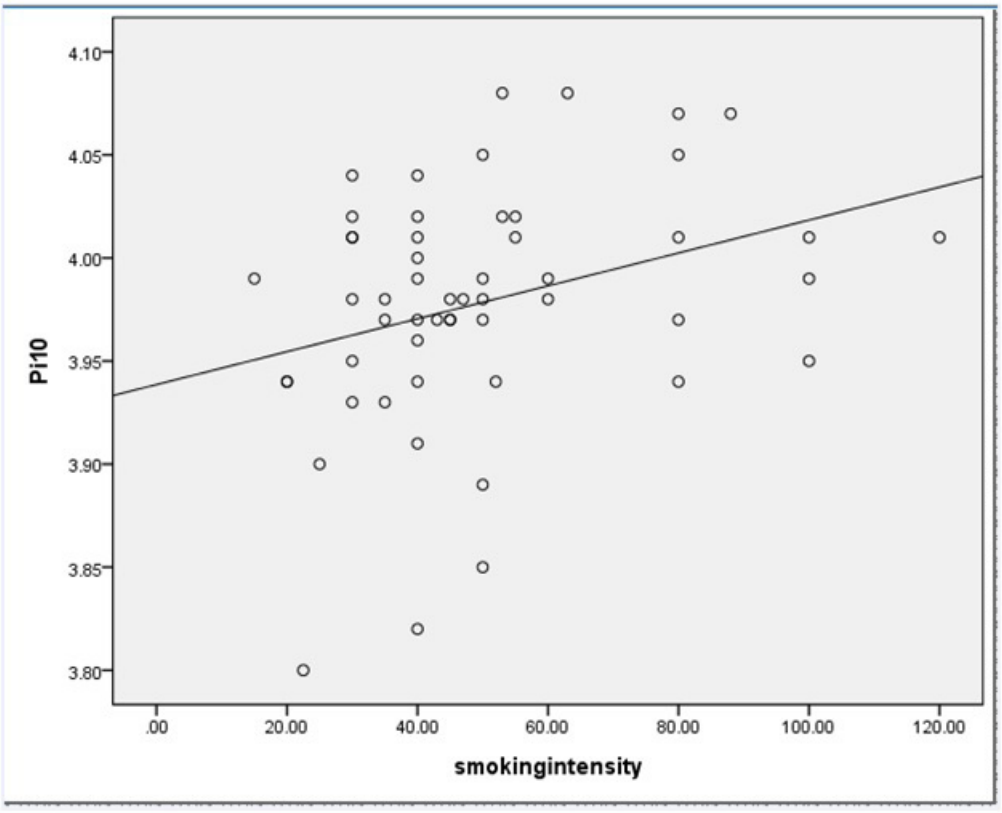

Figure 1A: The correlation between pack years and Pi10 (r=-0.474, P=0.002)

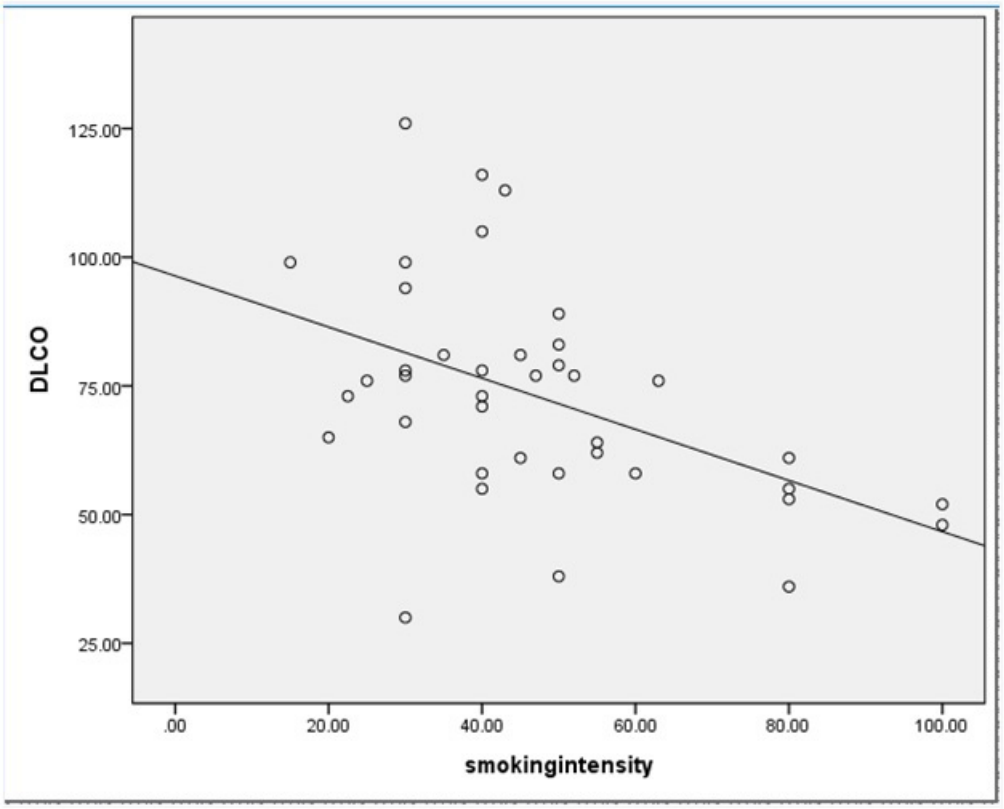

Figure 1B: The correlation between pack years and DLco(r=0.343, P=0.011).

5. Discussion

Our study revealed that the Pi10 increased as pack years increased, suggesting that airway remodeling had occurred although it was not indicated by the spirometry results. In previous studies, emphysematous regions and the average wall thickness, as quantified by CT, negatively associated with PFT results in COPD patients [10-14]. Reports have indicated that Pi10 independently contributes to airflow obstruction [10]. Grydeland et al. reported that clin-

ical symptoms such as coughing and wheezing were best predicted by Pi10 [15]. Additionally, because lung-function tests for characteristic abnormalities, such as spirometry, can produce normal results for CPFE patients, potential airway remodeling in CPFE patients without symptoms may go unnoticed. In our study, airway remodeling mainly occurred in CPFE patients with more than 50 pack years, which indicates that only heavy pack years plays an important role in the airway changes in CPFE.

The PFT results of CPFE patients are usually within the normal range, with the exception of DLco, which is often severely reduced. It is not easy, however, to repeatedly measure the decrease in DLco in pulmonary function, the leading cause of respiratory distress in CPFE patients in clinical. Our study revealed a negative association between pack years and the DLco in which the DLco was reduced in individuals with more pack years, and this finding is in line with a previous report [16]. The extent of fibrosis more significantly affects DLco than the severity of emphysema [5]. Also, Pi10 previously correlated with the DLco in COPD patients, and the inflammatory and airway remodeling in the vessels adjacent to the bronchi may play a more important role in COPD than in emphysema alone [17]. Therefore, we speculate that the Pi10 measurements may also associate with reduced DLco in CPFE patients with a more severe inflammatory condition. If Pi10 is abnormally increased on quantitative chest CT, it is thought that it can provide the basis for recommendation of DLco in PFT.

There are some limitations to our study. First, the pack years and smoking status were retrospectively acquired, which may have caused information bias. Additionally, given the small sample size, the influence of certain extrema cannot be excluded. Second, as this is the first presentation of Pi10 measures in patients with CPFE patients we recommend caution in the interpretation of these findings. Then, future longitudinal assessments of Pi10 would be needed.

In conclusion, we found that increased Pi10, as measured by QCT, and severely decreased DLco occurred most often in CPFE patients with more than 50 pack years. Because it is well known that segmental airway wall thickening on QCT may provide a marker of smoking-related airway injury, Pi10 measured by QCT, also, would be a clinically relevant biomarker of smoking-related airway injury in cumulative cigarette smoking.

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