



Quantitative CT Analysis Based on Smoking Habits and Chronic Obstructive Pulmonary Disease in Patients with Normal Chest CT

정상 흉부 단층촬영 검사에서 흡연 및 폐쇄성 폐질환 유무에 따른 정량화 검사 분석

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Purpose To assess normal CT scans with quantitative CT (QCT) analysis based on smoking habits and chronic obstructive pulmonary disease (COPD).

Materials and Methods From January 2013 to December 2014, 90 male patients with normal chest CT and quantification analysis results were enrolled in our study [non-COPD never-smokers ($n = 38$) and smokers ($n = 45$), COPD smokers ($n = 7$)]. In addition, an age-matched cohort study was performed for seven smokers with COPD. The square root of the wall area of a hypothetical bronchus of internal perimeter 10 mm (Pi10), skewness, kurtosis, mean lung attenuation (MLA), and percentage of low attenuation area (%LAA) were evaluated.

Results Among patients without COPD, the Pi10 of smokers (4.176 ± 0.282) was about 0.1 mm thicker than that of never-smokers (4.070 ± 0.191 , $p = 0.047$), and skewness and kurtosis of smokers (2.628 ± 0.484 and 6.448 ± 3.427) were lower than never-smokers (2.884 ± 0.624 , $p = 0.038$ and 8.594 ± 4.944 , $p = 0.02$). The Pi10 of COPD smokers (4.429 ± 0.435 , $n = 7$) was about 0.4 mm thicker than never-smokers without COPD (3.996 ± 0.115 , $n = 14$, $p = 0.005$). There were no significant differences in MLA and %LAA between groups ($p > 0.05$).

Conclusion Even on normal CT scans, QCT showed that the airway walls of smokers are thicker than

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never-smokers regardless of COPD and it preceded lung parenchymal changes.

Index terms Chronic Obstructive Pulmonary Disease; Cigarette Smoking; Spiral Cone-Beam Computed Tomography; Quantitative CT

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is reported to be 1% at all ages and is estimated to be the third leading cause of death by 2020 (1, 2). In addition, interest in COPD screening has increased because most patients with COPD are not being diagnosed (3). Grade I or II COPD was defined as $FEV_1 > 50\%$ (4). Efforts have been made to stop progression because some of them could be progressed to severe stage. Among clinical trials on mild and moderate COPD, lung health study reported the most important way to prevent COPD progression as smoking cessation (4). Unfortunately, there is lack of evidence as to whether smoking cessation increases due to COPD screening. However, if the impact of smoking is objectively indicated on CT, it may motivate patients to quit smoking. Furthermore, if smokers with mild to moderate COPD could be found among smokers who had normal CT scans, it will also help COPD screening.

Quantitative CT (QCT) studies focusing on with COPD often attempted to quantify emphysema or bronchial wall thickness or to identify the effects of smoking (5-7). The emphysema and air trapping of COPD features were quantified by QCT parameters such as percentage of low attenuation areas (%LAA) on inspiration or expiration CT (6). The airway abnormality of COPD was most commonly measured by the square root of wall area (WA) of a hypothetical bronchus of internal perimeter 10 mm, calculated from linear regression of all measured bronchi, referred as $Pi10$ (6). In the past study, the sex, age and smoking composition of the study population has strong effects on the QCT measurements above (7). However, never-smokers were not included in the above study. Also there were few QCT studies for normal CT scans because study population was usually decided by smoking history (smoker and non-smoker) or presence of COPD disease (COPD or non-COPD).

In clinical practice, many CT scans are often read normally even if patients, regardless of smoking history, had symptoms such as chronic cough or dyspnea. Some of them may be mild or moderate COPD patients, but they cannot be identified without spirometry results. If QCT provide negative effect of smoking for those patients, stronger recommendation for smoking cessation could be made even though they had normal CT. Furthermore, mild to moderate COPD could be found with QCT for smokers with normal CT. The purpose of this study was to assess normal CT scans with QCT analysis according to smoking habit and COPD.

MATERIALS AND METHODS

This study was a retrospective analysis by reviewing the patient's medical records after applying for exemption from the consent form and receiving approval from the clinical examination committee (IRB No. 2022-09-041).

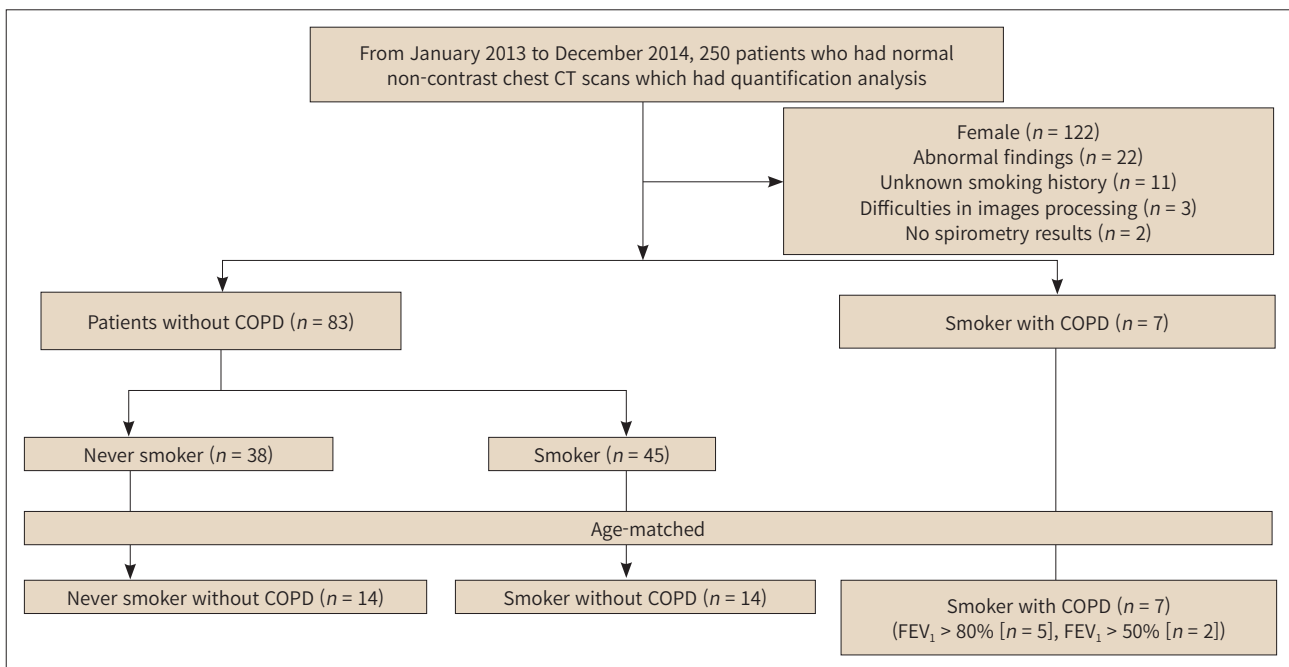
PATIENTS AND STUDY DESIGN

From January 2013 to December 2014, 250 patients who had not only non-contrast chest CT with normal finding but also quantification analysis at Jeonbuk National University Hospital were enrolled. The patients underwent chest CT scans due to reasons as follows: 1) respiratory symptoms (73%, $n = 183$) and 2) lung cancer screening without respiratory symptoms (27%, $n = 67$). The following patients were excluded from the study after CT review: 1) female patients due to gender difference in QCT parameters between female and male patients ($n = 122$), 2) patients with abnormal CT findings by visual assessment such as definite airway wall thickening and abnormal attenuation of lung ($n = 22$), 3) patients without accurate smoking history ($n = 11$), 4) patients who had difficulty in imaging processing at QCT ($n = 3$). 5) patients without spirometry results ($n = 2$). Finally, 90 male subjects were enrolled in this study. For subgroup analysis for COPD smokers, age-matched controlled study was also performed (Fig. 1).

For evaluation of difference between never smokers and smokers among patients without COPD, comparison of results of pulmonary function test (PFT) and QCT was performed. Patients with PFTs were compared such as forced expiratory volume in 1 second (FEV_1), forced expiratory flow at 25%–75% ($FEF_{25\%-75\%}$), forced vital capacity (FVC), and FEV_1/FVC ratio.

For reducing effects of ages and smoking habit, the patients without COPD were classified as follows. They were classified as younger (≤ 40), middle-aged (41–60), and elderly group (≥ 61) according to age. The smokers without COPD were divided into the following groups according to smoking intensity regardless of current or ex-smoker: group I (pack-years < 10), group II ($10 \leq$ pack-years < 30), group III (≥ 30 pack-years).

Fig. 1. Flowchart of study population.



COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second

COMPUTED TOMOGRAPHY TECHNIQUE

All CTs were performed according to the COPDGENE study protocol (8) using 128 channels (Somatom Definition Flash, Siemens Medical Solution, Erlangen, Germany). All patients were taken at full inspiration (200 mAs). The tube current was 120 kVp, the rotation time was 0.28 seconds, the slice thickness was 1 mm, and the reconstruction interval was 1 mm.

A B35f reconstruction kernel was used and the collimation was 128×0.6 mm. All photographed images were evaluated after setting in a lung window: window level (-600 to -700 Housefield unit [HU]), window width (1200–1500 HU).

PULMONARY QUANTIFICATION ANALYSIS

Quantitative analysis of airways and lung parenchyma was performed semi-automatically using a commercially available image processing program (VIDA Apollo, version 1.2; Vida Diagnostics, Coralville, IA, USA). Airway segmentations obtained with the software were assessed for complete airway inclusion as well as correct and consistent labeling. Skipped branch points were manually added as necessary to ensure accurate measurement of airway length.

The lung quantification parameter such as The square root of WA of a hypothetical bronchus of internal perimeter 10 mm (Pi10), skewness, kurtosis, and mean lung attenuation (MLA), percentage of %LAA were obtained. The Pi10 value was obtained as a global comparative measure using 6 segmented airway branches and calculated from linear regression of all measured bronchi. When histograms were obtained by measuring the number of pixels according to the attenuation coefficient of CT, the kurtosis and skewness were obtained automatically by the program. The MLA was obtained by calculating the average attenuation coefficient of the lung voxels. In this study, MLA of both lungs taken during inspiration was used for the analysis. The %LAA was defined as the fraction of the area in which the attenuation value is smaller than -950 HU in the inspiration image.

STATISTICAL ANALYSIS

The continuous and parametric variables, which were equally distributed, were compared using the independent samples *t* test and the one-way ANOVA. Mann-Whitney U test and Kruskal-Wallis test were used for nonparametric variables. The normal distribution test was performed using the Kolmogorov-Smirnov test. SPSS version 12.0.1 (SPSS, Chicago, IL, USA) was used and the *p* value was considered to be significant when the *p* value was less than 0.05.

RESULTS

There were patients without COPD (92.2%, 83 males) and 7 COPD patients (7.8%, 7 males) were classified after we reviewed the PFT. 7 COPD patients was grade I ($n = 5$) to grade II ($n = 2$) according to GOLD stage (9).

Of the 83 patients without COPD, 45 (54.2%) were smokers and 38 (45.8%) were never smokers. The mean age was 50.9 years (range, 18–79 years). Among 45 smokers, 25 smokers (55.6%) were current smokers and 20 smokers (44.4%) were ex-smokers. Average amount of smoking was 21.7 pack years. Among patients with COPD disease, the mean age of these patients was 64.9 (range, 49–76) years old. They were all smokers and the average smoking amount was

Table 1. Comparison of Patients without COPD Based on Smoking Habits

	Never Smoker without COPD (n = 38)	Smoker without COPD (n = 45)			p-Value	Smoker without COPD (n = 45)			p-Value			
		Smoker without COPD (n = 45)	Group I (< 10 PY, n = 6)	Group II (10 ≤ PY < 30, n = 25)		Group III (≥ 30 PY, n = 14)	p-Value I vs. II	p-Value II vs. III		p-Value I vs. III		
Age, mean	52.7 [18-79]	49.4 [25-79]	36.0 [27-64]	47.4 [25-79]	0.312	0.033	0.148	58.5 [50-68]	0.248	0.075	0.007	0.006
PY	0	21.7 [0.4-70]	4.7 [0.4-9]	17.2 [10-25]	N/A	N/A	N/A	37.0 [30-70]	N/A	0.000	0.000	0.000
FVC, %	92 ± 12.8	93 ± 10.9	85 ± 4.6	94 ± 12.2	0.718	0.047	0.638	96 ± 8.9	0.536	0.008	0.604	0.012
FEV ₁ , %	100 ± 12.3	100 ± 10.7	93 ± 5.1	100 ± 12.1	0.829	0.087	0.955	103 ± 8.4	0.403	0.148	0.478	0.013
FEV ₁ /FVC	80 ± 5.3	80 ± 5.9	85 ± 5.4	80 ± 6.7	0.945	0.057	0.933	78 ± 2.8	0.165	0.134	0.102	0.001
FEF _{25%-75%} , %	94 ± 19.5	94 ± 19.3	100 ± 25.9	94 ± 20.2	0.922	0.561	0.653	91 ± 14.7	0.733	0.498	0.641	0.306
Pi10, mm	4.070 ± 0.191	4.176 ± 0.282	3.972 ± 0.246	4.197 ± 0.293	0.047	0.305	0.084	4.225 ± 0.256	0.013	0.130	0.553	0.041
Skewness	2.884 ± 0.624	2.628 ± 0.484	2.733 ± 0.390	2.700 ± 0.533	0.038	0.538	0.216	2.454 ± 0.401	0.016	0.841	0.198	0.138
Kurtosis	8.594 ± 4.944	6.448 ± 3.427	7.290 ± 2.506	6.905 ± 3.989	0.027	0.682	0.119	5.271 ± 2.395	0.015	0.516	0.266	0.099
MLA, HU	-840 ± 27	-829 ± 25	-810 ± 30	-835 ± 26	0.084	0.029	0.440	-827 ± 20	0.127	0.047	0.332	0.146
%LAA	1.859 ± 3.684	0.971 ± 1.876	0.443 ± 0.791	1.276 ± 2.385	0.075	0.194	0.160	0.655 ± 0.872	0.240	0.411	0.250	0.616

Data are mean ± standard deviation, with range in parentheses.

COPD = chronic obstructive pulmonary disease, FEF_{25%-75%} = forced expiratory flow at 25%-75%, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, HU = Housefield unit, %LAA = low attenuation area, MLA = mean lung attenuation, N/A = not applicable, Pi10 = airway wall thickness for an airway with an internal perimeter of 10 mm, PY = pack-years

20.5 pack years. To evaluate the possibility to find COPD to use QCT on chest CT in those patients, we matched age of 7 smokers with COPD. 14 smokers and 14 never smoker among normal subjects were randomly selected as matched controls to compare QCT and PFTs with those of smoker with COPD (Fig. 1).

Table 1 showed comparison between never smokers and smokers among patients without COPD according to smoking habit. Pi10 of smokers without COPD was 0.1 mm thicker than that of never smokers without COPD (4.176 ± 0.282 mm vs. 4.070 ± 0.191 mm, $p = 0.047$). Especially, the Pi10 of group III (more than 30 pack years) of smokers without COPD was about 0.2mm thicker than that of never smokers without COPD (4.225 ± 0.256 mm vs. 4.070 ± 0.191 mm, $p = 0.013$). However, there were no significant differences when group I or II compared with never smokers without COPD. Skewness (2.628 ± 0.484) and kurtosis (6.448 ± 3.427) of smokers without COPD were lower than those of never smoker without COPD (skewness: 2.884 ± 0.624 , $p = 0.038$, kurtosis: 8.594 ± 4.944 , $p = 0.027$). Group III smokers had significantly higher skewness (2.454 ± 0.401) and kurtosis (5.271 ± 2.395) compared with those of never smoker without COPD (2.884 ± 0.624 , $p = 0.016$, kurtosis: 8.594 ± 4.944 , $p = 0.015$). FVC, FEV₁, and FEV₁/FVC of group III smokers is significantly lower than that of group I smokers.

In the matched study, smokers with COPD had lower pulmonary function than other groups (Table 2). Smokers with COPD had largest Pi10 (4.427 ± 0.437) which was about 0.4 mm thicker than that of matched never smokers without COPD (4.001 ± 0.108 , $p = 0.005$) (Fig. 2). It was about 0.2 mm thicker than that of matched smokers without COPD (4.253 ± 0.192), but the difference was not statistically significant ($p = 0.346$). There were no significant differences in other QCT variables (Table 2). Fig. 2 showed the examples of 3D airway and Pi10 in never smokers without COPD and smoker with COPD.

Table 2. Quantitative CT Measurements of Never Smokers, Smokers without COPD, and Smokers with COPD

	(1) Never Smoker without COPD (n = 14)	(2) Smoker without COPD (n = 14)	(3) Smoker with COPD (n = 7)	(1) vs. (2) p-Value*	(1) vs. (3) p-Value*	(2) vs. (3) p-Value*	p-Value [†]
Age, median	61	61	63	0.643	0.834	0.520	0.843
PY	0	21 (median) [2-48]	20 (median) [0.7-45]	N/A	N/A	N/A	N/A
FVC, %	90 ± 13.0	95 ± 12.5	94 ± 8.8	0.374	0.481	0.936	0.640
FEV ₁ , %	99 ± 11.6	101 ± 11.9	87 ± 10.6	0.590	0.030	0.013	0.013
FEV ₁ /FVC	79 ± 4.4	77 ± 3.5	65 ± 5.8	0.199	<0.001	<0.001	0.000
FEF _{25%-75%} , %	91 ± 18.4	87 ± 16.1	50 ± 10.8	<0.001	<0.001	<0.001	0.000
Pi10, mm	4.001 ± 0.108	4.253 ± 0.192	4.427 ± 0.437	<0.001	0.042	0.346	0.005
Skewness	2.872 ± 0.696	2.827 ± 0.520	2.612 ± 0.370	0.848	0.277	0.342	0.607
Kurtosis	8.518 ± 5.290	7.716 ± 3.955	5.903 ± 2.094	0.654	0.123	0.274	0.473
%LAA	2.069 ± 3.619	0.716 ± 1.254	1.816 ± 3.275	0.205	0.878	0.275	0.539
MLA, HU	-840 ± 22	-831 ± 28	-851 ± 20	0.360	0.284	0.109	0.572

Data are mean ± standard deviation, with range in parentheses. p values were calculated using.

*Mann-Whitney U test.

†Kruskal-Wallis test.

COPD = chronic obstructive pulmonary disease, FEF_{25%-75%} = forced expiratory flow at 25%-75%, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, HU = Housefield unit, %LAA = low attenuation area, MLA = mean lung attenuation, N/A = not applicable, Pi10 = airway wall thickness for an airway with an internal perimeter of 10 mm, PY = pack-years

Fig. 2. 3D airway and Pi10 of never-smokers without COPD and smokers with grade II COPD.

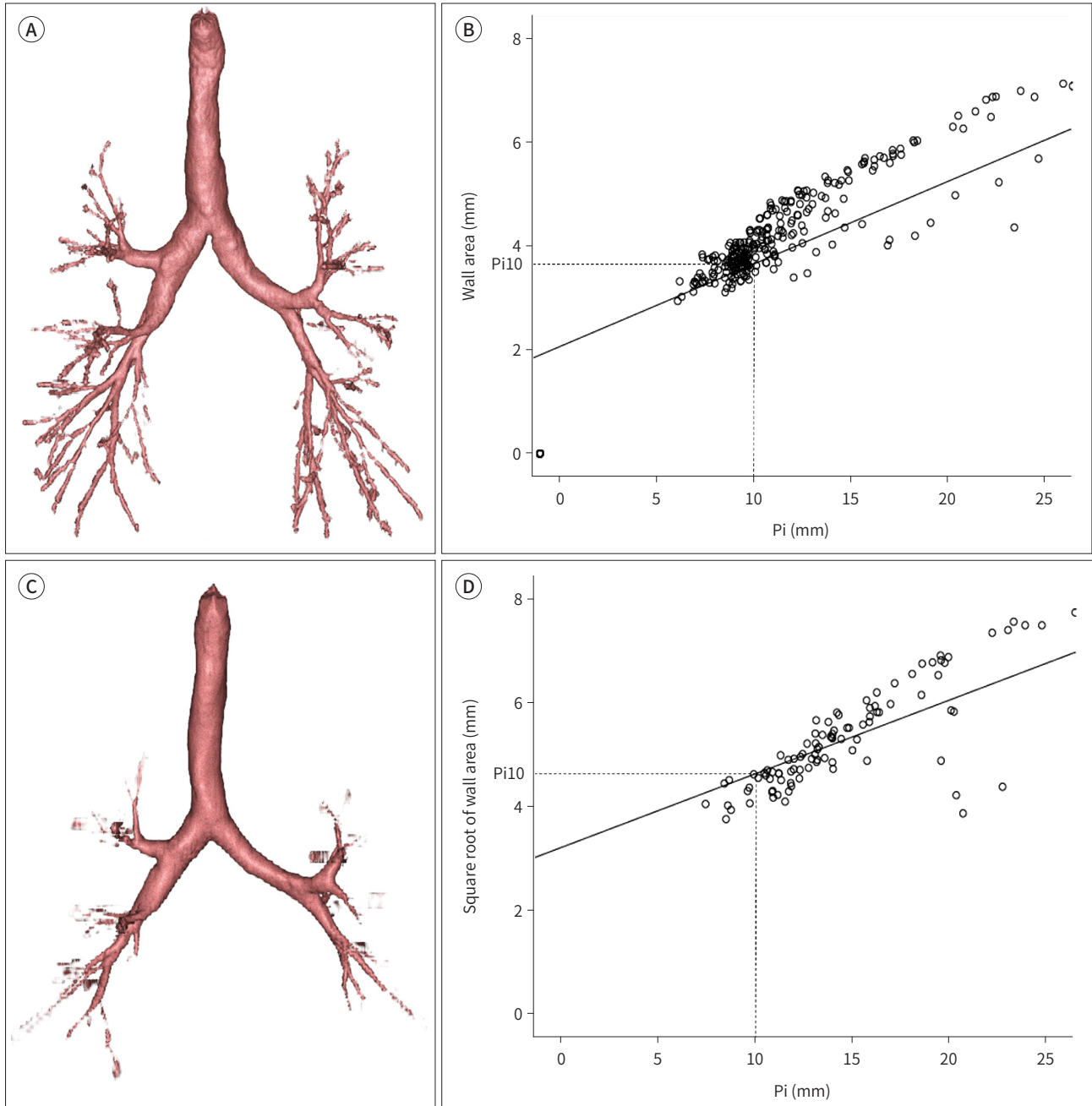
A. 3D airway of a 48-year-old male, (never smoker and without COPD) that is well-detailed and abundant.

B. Pi10 is 3.96 mm. The spirometry results are as follows: FEV₁/FVC, 88%; FEV₁, 90% (2990 mL); FEF_{25%-75%}, 126%; and FVC, 77% (3410 mL).

C. Image of a 53-year-old male smoker with grade II COPD and with a smoking history of 20 pack-years. The quality of the 3D airway was poor and had scarce branches.

D. Pi10 is 4.77 mm. The spirometry results are as follows: FEV₁/FVC, 68%; FEV₁, 75% (2260 mL); FEF_{25%-75%}, 41%; and FVC, 82% (3340 mL).

COPD = chronic obstructive pulmonary disease, FEF_{25%-75%} = forced expiratory flow at 25%–75%, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, Pi = The square root of the wall area of a hypothetical bronchus of internal perimeter



DISCUSSION

This study showed that smokers without COPD had thicker airway with never smokers without COPD even though they all had normal CT scans. In addition, smokers with grade I-II COPD had thicker airway than never smokers without COPD and there was no difference in other QCT variables. It showed the possibility that airway changes would be faster than changes in lung parenchyma.

This study showed heavy smokers, who had smoking history of 30 packs years or more, had thicker airway than never smokers and light smokers, who had smoking history of less than 10 packs years even though they had no COPD. This result is similar to that reported previously (7, 10, 11). Grydeland et al. (7) reported that Pi10 increased with number of pack-years in controls, while %LAA increased with number of pack-years in COPD cases, after adjusting for sex, age and daily cigarette consumption. Donohu et al. (11) reported that long-term cigarette smoking was associated with subclinical increases in wall thickness of sub-segmental airways. Patel et al. (10) also reported an association between Pi10 and pack years ($r = 0.26$). However, Kim et al. (12) reported that there is no difference in the QCT parameters in normal subjects according to smoking habits. This is probably because they define the heavy smokers as smokers who had smoking history of 20 packs years or more. When these results were considered, 30 packs years or more smoking history may be needed to change noticeably airway wall thickness in smokers without COPD who have normal CT.

In this study, there were no significant difference between smokers with COPD and smokers without COPD. Similarly, Berger et al. (13) has been reported that the WA is not different between smokers with COPD and smokers without COPD. Koo et al. (14) reported that airway and parenchymal attenuation parameters are independent predictors of pulmonary function in patients with grade I and II COPD, whereas parenchymal attenuation parameters are dominant independent predictors of pulmonary function in patients with grade III and IV COPD. However, it is well known that smokers without COPD also could have bronchial inflammation causing airway wall thickening (15-17). It is well known that the inflammatory response to smoking can increase attenuation of lung parenchyma enough to mask emphysema (18, 19). This suggest that inflammation induced by smoking could make difficult to screen grade I or II COPD within smokers with normal CT.

Skewness and kurtosis are usually known to be associated with pulmonary fibrosis because kurtosis or skewness of CT densitometry in the lung has focused on interstitial lung disease studies (20, 21). Yamashiro et al. (22) studied inspiratory and expiratory skewness and kurtosis of 46 smokers with COPD. They concluded that higher expiratory values and the higher expiratory/inspiratory ratios of kurtosis and skewness reflect more severe airflow limitation and air-trapping in COPD. The difference of this study from the above studies is only patients with normal CT were enrolled therefore emphysema or fibrosis was not evident. In addition, parameters on expiratory CT were not analysed in this study. Although normal CT scans were analysed, heavy smokers (> 30 pack-years) had significantly lower skewness (non-smokers: 2.884 ± 0.624 vs. heavy smokers: 2.454 ± 0.401 , $p = 0.016$) and lower kurtosis (non-smokers: 8.594 ± 4.944 vs. heavy smokers: 5.271 ± 2.395 , $p = 0.015$) than never smokers without COPD. This suggested that inflammation induced by smoking increase attenuation of lung parenchy-

ma and change lung parenchyma heterogeneously.

There were several limitations in this study. First, only men were compared and there was a limit statistical analysis because of the number of patients. It is well known that QCT parameters differ between female and male (7, 12). Although we tried to analyze male and female separately, we could not analyze female because only one female was a smoker. This is likely to require large-scale studies in the future. Second, Pi10 has the disadvantage that it does not reflect focal thickening of airway walls. However, it is not likely that the effect of smoking affected only part of the small airway. Therefore, Pi10 seems to be able to reflect the effect of smoking on small airways. Finally, the intra/inter-observer variability of the QCT analysis was not evaluated. However, previous studies have shown that the differences between manufacturers of CT can be solved by using similar scan and reconstruction parameters (23). It is also recommended that the same software for analysis when the lung attenuation was compared (24). This study used the same software, similar scans and reconstruction variables, so there intra/inter-observer variability is not likely to be large. Finally, there was no correction for body mass index.

In conclusion, the airway wall of smoker with/without mild to moderate COPD is thicker than non-COPD non-smokers even though they had normal CT. For smokers, the airway wall thickness may change faster than lung parenchyma.

Author Contributions

Conceptualization, B.J.H., J.G.Y.; methodology, B.J.H.; supervision, J.G.Y.; writing—original draft, B.J.H.; and writing—review & editing, H.Y.M., C.E.J., C.K.J., P.E.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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정상 흉부 단층촬영 검사에서 흡연 및 폐쇄성 폐질환 유무에 따른 정량화 검사 분석

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목적 정상으로 보이는 chest CT를 정량화 분석하여 흡연 및 폐쇄성 폐질환(chronic obstructive pulmonary disease; 이하 COPD) 여부에 따른 차이가 있는지 확인하고자 하였다.

대상과 방법 2013년 1월부터 2014년 12월까지 chest CT가 정상이면서 정량화 분석이 있는 90명의 남자 환자[COPD 없는 비흡연자($n = 38$)와 흡연자($n = 45$), COPD 흡연자($n = 7$)]를 대상으로 하였다. COPD 흡연자 7명을 대상으로 나이를 추출하여 환자-대조군 연구도 하위 분석하였다. Pi10, 왜도, 첨도, 평균감쇠계수, 저감쇠영역%와 같은 정량화 변수를 분석하였다.

결과 COPD가 없는 환자 중에서 흡연자의 Pi10 (4.176 ± 0.282 , $n = 45$)이 비흡연자에 비해 약 0.1 mm 정도 두꺼웠고(4.070 ± 0.191 , $n = 38$, $p = 0.047$), 흡연자의 왜도와 첨도(2.628 ± 0.484 and 6.448 ± 3.427)가 비흡연자보다 낮았다(2.884 ± 0.624 , $p = 0.038$ and 8.594 ± 4.944 , $p = 0.027$). COPD가 있는 흡연자들의 Pi10 (4.427 ± 0.437 , $n = 7$)이 COPD가 없는 비흡연자들보다 약 0.4 mm 두꺼웠다(4.001 ± 0.108 , $n = 14$, $p = 0.005$). 그러나 평균감쇠계수와 저감쇠영역%에서는 유의한 차이가 없었다.

결론 정상 chest CT를 보이더라도 QCT로 COPD의 유무와 상관없이 흡연자들의 소기도가 두꺼운 것을 알 수 있으며 이는 폐실질 변화보다 더 선형한다.

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