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Relationship between current smoking, visual CT findings and emphysema index in cigarette smokers

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ABSTRACT

Purpose: To evaluate whether visual CT findings could account for the effect of current smoking.
Methods: 500 CT scans were visually evaluated within each lobe. A multivariate model for emphysema index was constructed containing previously described confounders in addition to the visual components associated with smoking status.
Results: Current smokers displayed 23% less visual emphysema, 19% more airway wall thickening, and 188% more centrilogular nodule than former smokers (all $p < 0.001$). The effect of current smoking on the emphysema index decreased after adjustment with confounders and visual parameters.
Conclusions: Visual CT findings could partially account for the effect of current smoking.

Chronic obstructive pulmonary disease (COPD) is characterized by chronic slowly progressive, incompletely reversible airflow obstruction, associated with small airway remodeling and emphysema [1–3]. In COPD, noxious particles or gases are associated with an abnormal inflammatory response of the lungs, particularly the small airways [3,4]. One of major causes of inflammatory changes in the lungs is smoking [2–6]. Cessation of smoking is the best strategy for COPD treatment. Smoking cessation improves symptoms of COPD and reduces the rate of decline in lung function [6]. Lung function correlates with the extent of emphysema quantified subjectively or objectively through computed tomography (CT). The extent of emphysema increased on CT in subjects who continued to smoke, but did not in those who quit smoking [7,8].

Quantification of lung emphysema, by evaluating the extent of low attenuation areas is useful for evaluating disease severity and prognosis in patient with COPD [9–11]. Extent of emphysema is measured more reliably and accurately by quantitative computed tomography (QCT) than by subjective visual grading [12–14]. However, because quantitative CT cannot identify small amounts of emphysema, and cannot identify the pattern of emphysema, visual assessment is considered as complementary to QCT [5,12,13,15].

Recently, some studies reported that cessation of smoking increased the apparent extent of emphysema measured by QCT [8,16]. The reason is unclear, but reduction of inflammatory burden after smoking cessation is considered as the most likely cause of this paradoxical fall in lung density [16]. In a study of 6762 current and cigarette smokers, we recently showed that the mean percentage of low attenuation areas less than −950 HU was 3.5% lower in current smokers than in former smokers, after adjustment for disease severity and other factors [17]. We hypothesized that visible manifestations of smoking-related lung injury such as ground glass abnormality or centrilobular nodularity could account in part for the differences in CT attenuation parameters between current and former smokers. Therefore, in this study we evaluated whether visual CT findings could account for the effect of current smoking effect on low attenuation areas less than −950 HU, in a group of current and former smokers matched for disease severity.

1. Materials and methods

1.1. Subjects

Study subjects were selected from participants in the COPDGene Study in which 10,192 subjects were enrolled from 21 clinical study centers. All participants took inspiratory and expiratory CT scans, demographic and medical history questionnaires, and spirometry with

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other pulmonary function test [18]. The severity of COPD was classified according to GOLD Stage [19]. The analyses of the clinical and imaging data were approved by the institutional review board at each hospital, and written informed consent was obtained from all participants. This study was approved by the Executive Committee of the COPDGene study.

From the large COPDGene dataset, 100 smokers (50 current smokers and 50 former smokers) were randomly selected from each of the following categories by the data coordinating center of the COPDGene study: (a) smokers without evidence for COPD, (b) smokers with GOLD stage 1 COPD, (c) smokers with GOLD stage 2 COPD, (d) smokers with GOLD stage 2 COPD, (e) smokers with GOLD stage 3 COPD, (f) smokers with GOLD stage 4 COPD.

1.2. CT image acquisition

Whole-lung volumetric CT scans were performed at full inspiration and at the end of normal expiration. Before the CT scan, specific breathing instructions were provided to each subject. All CT scans were obtained with 120 kVp, 200 mAs for inspiration examination and 50 mAs for expiration examination. CT images were reconstructed with different slice thickness of 0.625, 0.75, and 0.9 mm and the corresponding slice intervals of 0.625, 0.5, and 0.45 depending on the parameters permitted by each scanner model [18,20]. Intravenous contrast medium was not used. Two sets of CT images were reconstructed with different reconstruction algorithm: (a) high frequency reconstruction algorithm for visual analysis, (b) smooth reconstruction algorithm for quantitative analysis [15].

1.3. Visual analysis of CT images

Two chest radiologists with 7 years of experience (S.S.J) and 12 years of experience (K.Y) performed visual analysis independently without knowledge of clinical history and pulmonary function information. Before the performance of visual analysis, 20 sets of CT images were analyzed as a preliminary assessment to improve concordance with regard to visual findings. CT scans of the 500 subjects were presented in random order, and observers were blinded to smoking status or GOLD stage. Readers used Aquarius Net program (TeraRecon, San Mateo, Calif) for visual analysis. The inspiration and expiration CT data with the high-frequency algorithm were presented for visual analysis. Reconstruction of multiplanar images was permitted. The CT images were evaluated at lung window settings (window level = −700 HU; window width = 1500), but adjustments were permitted.

Lobe-based quantitative visual analysis was performed for specific CT parameters. Six lobes including linguar segment were assessed for each case. For the evaluation of emphysema, readers marked the type of emphysema as centrilobular, panlobular, or mixed. Poorly marginated centrilobular nodules were considered as inflammatory nodules due to smoking (Fig. 1) [7,21,22]. The extent of emphysema, centrilobular nodules, ground glass opacity, air-trapping, reticular densities and honeycombing in each lobe and in the entire lung was assessed by using a six-point scale: 0%, 1%–5%, 6%–25%, 26%–50%, 51%–75%, and > 75% (range 0–5) [5]. Expiratory air-trapping were assessed by comparison of inspiration and expiration CT images. The presence of airway wall thickening, bronchiectasis, mosaic attenuation, and atelectasis was assessed in each lobe. Mosaic attenuation was defined lower attenuation above 25% of the lobe, excluding emphysema area on inspiratory CT.

1.4. Quantitative analysis

Quantitative analysis of emphysema extent was performed on images reconstructed with a standard algorithm, using open-source 3D Slicer software (http://www.slicer.org) which provided automated lung segmentations and densitometry measures. The density mask technique was employed with thresholds for lung attenuation set at −950 HU. Emphysema index was defined as voxels ≤ −950 HU on inspiratory scans and expressed as percentage of TLC_{CT} (total lung capacity measured by CT) [23].

1.5. Statistical analysis

Statistical differences in age, weight, height, smoking extent, FEV1/FVC ratio, FEV1 (%predicted), and TLC_{CT} between former smokers and current smokers were assessed by using the Mann-Whitney *U* test. Chi-square test was used to assess statistical differences in sex and race distribution between the two groups. In each category of GOLD stage, the difference of emphysema index between the two groups was assessed by using the Mann-Whitney *U* test. The Cohen kappa statistic was used to assess the agreement for type of emphysema between two readers. Inter-reader agreement for visual assessment of CT parameters was evaluated by using the weighted kappa statistics.

The visual extent of emphysema, centrilobular nodules, ground glass opacity, air trapping, reticular densities and honeycombing was calculated by adding the six-point scale scores in six lobes (range 0–30) and the visual extent of airway wall thickening, bronchiectasis, mosaic attenuation and atelectasis by counting the number of lobe seen each finding (range 0–6). The mean scores of data obtained by two radiologists were used for statistical analysis. Mann-Whitney *U* test was used to assess the statistical differences of visual scores of CT parameters between former smokers and current smokers. The correlation between visual extent of emphysema and quantitative CT was assessed by using simple regression analysis.

To reduce the effect of smoking status on emphysema index, multiple regression analysis was used. In Model 1, clinical confounding factors were adjusted. In model 2, visual extent of emphysema was added to adjust and in model 3, other significant visual CT parameters were added. All statistical analyses were obtained by SAS, version 9.3 (SAS Institute, Cary, NC). A p value of < 0.05 was considered statistically significant.

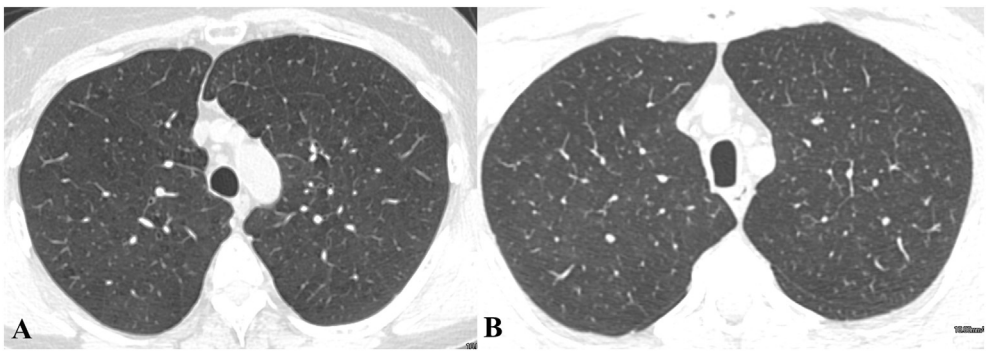

Fig. 1. A. Former smoker with GOLD stage 2 COPD. Mild centrilobular emphysema is noted in both lungs. Poorly marginated centrilobular nodule and airway wall thickening are not seen.
B. Current smoker with GOLD stage 2 COPD. Poorly marginated centrilobular nodules are seen in both lungs. Both readers assessed the visual extent of centrilobular nodules as > 75%. Also, airway walls were analyzed as thickened by two readers. There is no emphysema. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographics and physiologic characteristics of the study groups.

	Former smokers (n = 250)	Current smokers (n = 250)	p-Value
Age	66.0 ± 7.9 (66.4)	59.6 ± 8.0 (59.3)	< 0.0001
Sex (M:F)	129:121	137:113	0.4734
Race			
White:African American	225:25	177:73	< 0.0001
Weight (kg)	79.5 ± 18.1	78.3 ± 17.5	0.4555
Height (cm)	169.2 ± 9.3	170.1 ± 9.3	0.1863
Smoking			
Duration	36.4 ± 11.7	43.1 ± 8.6	< 0.0001
Pack-years	48.8 ± 27.9	50.1 ± 26.2	0.3280
FEV1/FVC ratio	0.54 ± 0.18	0.56 ± 0.17	0.1868
FEV1 (%predicted)	63.1 ± 30.0	63.3 ± 28.9	0.9785
TLC_{CT}	6.09 ± 1.45	5.94 ± 1.52	0.2350

Note – Data are mean ± SD. FEV1/FVC = ratio of FEV1 to forced vital capacity, FEV1 = forced expiratory flow in 1 s, TLC_{CT} = total lung capacity measured by CT.

2. Results

Among the study subjects, the current smokers were on average younger, had longer duration of cigarette smoking, and were more likely to be African American than former smokers (Table 1). However, the cigarette consumption in pack-years was not significantly different between former and current smokers. Other clinical parameters were not different between former and current smokers. In the former smokers, the mean (± standard deviation) interval since quitting smoking was 12.5 ± 10.6 years (Range 0–43 years).

On QCT of assessment, the former smokers displayed an emphysema index 5.5% higher than current smokers (Table 2). This difference was evident in each stratum of severity assessed by GOLD grade. The emphysema index increased with increasing severity of GOLD grade in both former and current smokers, except between GOLD stages 1 and 2.

Agreement between the two readers for the type of emphysema was moderate (k = 0.51). The overall extent of emphysema showed good agreement between two readers (k = 0.64), and moderate agreements was found for the extent of centrilobular nodules (k = 0.55) and airway wall thickening (k = 0.54).

The visual extent of emphysema was correlated with the emphysema index ($r = 0.82$, $p < 0.001$). The visual extent of emphysema, centrilobular nodules, airway wall thickening and reticular density all showed statistically significant differences between former and current smokers (Table 3). The mean visual extent of centrilobular nodules was 5.1 in GOLD stage 0; 5.3 in GOLD stage 1; 5.6 in GOLD stage 2; 3.7 in GOLD stage 3; 1.3 in GOLD stage 4.

After adjusting for potential confounders and for clinical indices of disease severity, multivariate analysis showed that the effect of current smoking on the emphysema index persisted (Table 4, Model 1). Since the visual extent of emphysema was slightly greater in the former smokers compared with current smokers, we constructed a second model (Model 2), which included adjustment for the visual extent of emphysema; the effect of smoking status persisted, though decreased ($\beta = -0.5$, $p < 0.001$). In Model 3, which adjusted for significant visual CT parameters, the effect of smoking status decreased even more ($\beta = -0.41$, $p < 0.001$) (Table 5).

Table 2
Mean emphysema index by GOLD stage and smoking status.

	N	Emphysema index ± SD		p-Value
		Former smoker	Current smokers	
Controls	100	2.9 ± 3.2	1.4 ± 1.6	0.0104
GOLD 1	100	9.7 ± 8.3	5.0 ± 5.7	0.0004
GOLD 2	100	9.5 ± 9.3	5.3 ± 6.1	0.0053
GOLD 3	100	17.7 ± 10.9	11.3 ± 13.1	0.0005
GOLD 4	100	30.7 ± 13.1	20.1 ± 13.7	0.0002
Total	500	14.1 ± 13.5	8.6 ± 3.4	< 0.0001

Table 3
Weighted Kappa values for sum scores.

CT parameters	Weighted Kappa
Emphysema	0.640
Centrilobular nodules	0.551
Ground-glass opacities	0.412
Air-way wall thickening	0.540
Bronchiectasis	0.115
Mosaic perfusion	0.448
Air-trapping	0.252
Reticular densities	0.274
Honeycombing	−0.0029
Atelectasis	0.473

Table 4
Visual extent of CT findings in current versus former smokers.

	Mean ± SD		p-Value
	Former smokers	Current smokers	
Visual emphysema	10.3 ± 8.6	8.0 ± 6.9	0.0114
Centrilobular nodules	2.2 ± 4.6	6.3 ± 7.8	< 0.0001
Ground-glass opacities	0.6 ± 1.8	0.9 ± 3.0	0.6290
Air-way wall thickening	3.7 ± 2.4	4.4 ± 2.2	0.0003
Bronchiectasis	0.46 ± 0.96	0.35 ± 0.85	0.1479
Mosaic attenuation	0.30 ± 1.09	0.34 ± 0.93	0.1357
Air-trapping	2.6 ± 3.8	2.2 ± 3.3	0.5477
Reticular densities	0.38 ± 1.05	0.22 ± 0.74	0.0439
Honeycombing	0.004 ± 0.04	0.02 ± 0.27	0.9952
Atelectasis	1.55 ± 1.36	1.34 ± 1.29	0.0855

Note – The visual extent of emphysema, centrilobular nodules, ground glass opacity, air trapping, reticular densities and honeycombing are calculated by adding the six-point scale score in six lobes (range 0–30) and the visual extent of airway wall thickening, bronchiectasis, mosaic attenuation and atelectasis by counting the number of lobe seen each finding (range 0–6).

3. Discussion

This study showed that current smoking status is associated with higher extent of centrilobular nodules and airway wall thickening, presumably reflecting increased levels of pulmonary and airway inflammation. In this study as in others, the subjective visual extent of emphysema was correlated highly with emphysema index affected [24]. Additionally, on multivariate analysis, visual extent of emphysema was found to be a significant predictor of quantitative emphysema score, even after adjustment for other important variables. Furthermore, as in previous studies [8,16,25], the emphysema index was relatively decreased in current smokers, even after adjustment for confounding factors. The current smoking effect persisted after adjustment for difference in severity of visual extent of emphysema, and decreased after further adjustment for extent of centrilobular nodules and airway wall thickening, suggesting that these visual manifestations of smoking related lung injury may account in part for the current smoker effect.

Progression of emphysema is detected more sensitively using lung densitometry than by using lung function parameters [9,15]. Recent studies [8,16] reported that smoking cessation results in apparent rapid progression of “emphysema” measured by QCT, and that smoking relapse increases lung density. Shaker et al. [16] reported that the apparent extent of emphysema was increased about 2.6% following at one year after smoking cessation. This phenomenon is considered likely to be due to reduced inflammatory burden and decreased sputum production after smoking cessation [16]. In accord with those studies, this study demonstrated that former smokers displayed about 5.5% more

Table 5
Multiple regression analysis for emphysema index.[a]

	Model 1[b]		Model 2		Model 3	
	$\hat{\beta}$	*p*-Value	$\hat{\beta}$	*p*-Value	$\hat{\beta}$	*p*-Value
Current smoker	−0.756	< 0.0001	−0.505	< 0.0001	−0.415	< 0.0001
Age	0.010	0.1004	0.007	0.2135	0.004	0.4952
Sex	0.056	0.6751	−0.095	0.3930	−0.169	0.1289
Race	0.587	< 0.0001	0.185	0.1231	0.186	0.1148
Pack ∗ year	0.0002	0.8947	−0.002	0.1731	−0.001	0.4549
Weight (kg)	−0.018	< 0.0001	−0.008	0.0039	−0.009	0.0011
Height (cm)	−0.018	0.0455	−0.018	0.0152	−0.018	0.0109
FEV1%	−0.005	0.1887	−0.003	0.2688	−0.006	0.0845
FEV1/FVC	−5.099	< 0.0001	−1.813	0.0045	−1.975	0.0019
TLC_{CT}	0.483	< 0.0001	0.350	< 0.0001	0.341	< 0.0001
Visual emphysema			0.121	< 0.0001	0.115	< 0.0001
Centrilobular nodule					−0.016	0.0126
Airway wall thickening					−0.070	0.0011
Bronchiectasis					0.017	0.6957
Mosaic perfusion					0.023	0.5626
Reticular densities					0.001	0.9905
Atelectectasis					0.038	0.2122
R^2	0.6925		0.7918		0.8018	

Model 2: Model including clinical confounding factors and visual emphysema.
Model 3: Model including clinical confounding factors, visual emphysema and other visual variables that differed significantly by smoking status ($P < 0.2$ for screening by Fisher, 1991).
[a] Square root of emphysema index was regressed due to non-normality on residuals.
[b] Model 1: Model including clinical confounding factors.

emphysema than current smokers on QCT. It is likely that at least some of this apparent difference is because subjects with more severe emphysema may have quit because of their lung disease, and therefore will be over-represented among the former smokers. We adjusted for this "healthy smoker effect" by stratifying the subjects according to GOLD stage, and indeed the spirometric measures of disease severity were very similar between the current and former smokers. Furthermore, the difference in emphysema index persisted when we included indices of disease severity in the multivariate analysis (Model 1), and when we subsequently adjusted for the slightly higher severity of visual emphysema in the former smokers (Model 2). It is interesting that the difference in emphysema index between former and current smokers was smaller in the control group than in those with COPD. This may be because of a greater degree of inflammation in subjects with more advanced COPD [2].

Inflammatory reactions induced smoking are present without tissue destruction or fibrosis and could be largely reversible [4,26–28]. In asymptomatic subjects, emphysema, ground-glass attenuation and ill-defined centrilobular nodularity are related to smoking [7]. Continued smoking worsens those findings [7]. Nodules indicate the presence of respiratory bronchiolitis, and ground-glass attenuation suggests the inflammation and fibrosis [27]. It has been reported that centrilobular nodularity decreased in prevalence with increasing severity of GOLD grade because the nodules are replaced by parenchymal destruction [29]. Other studies postulated that a greater increase in emphysematous lesions may conceal centrilobular nodules and ground-glass attenuation [30].

There has not to our knowledge been a previous study that documented differences in visual CT appearances between current and former smokers. In the present study, visual scores of centrilobular nodularity, and airway wall thickening were higher in the current smokers, compatible with smoking related bronchiolitis and respiratory bronchiolitis. It is a little surprising that the extent of ground glass abnormality was not significantly different between the two groups. This may be because the overall extent of ground glass abnormality in these subjects was relatively slight. It is also interesting that the extent of reticular densities was slightly higher in current smokers than those in former smokers. This may reflect the known association between cigarette smoking and lung fibrosis.

There were some limitations of this study. First, visual quantification is accompanied by observer variation [12,23]. Good agreement is seen in this study for visual quantitative analysis of emphysema, similar to other studies in which weighted kappa was used and preliminary assessment was performed [5,12,14,29]. Agreements of other CT parameters were fair or moderate agreement. The agreements of reticular density and honeycombing were low. In this study, subjects with pulmonary fibrosis were excluded. So, it was difficult to detect subtle reticular density and honeycombing on supine scan. Also, it was identified that low kappa value is obtained in study with high or low prevalence [29,31]. Recent study shows more increased agreement by using standard images [5]. For more accurate and reproducible quantification, objective quantitative measurements of other CT parameters are needed. Second, there were a 6.3 year difference in age between the current and former smokers. The normal airspace enlargement of aging may have contributed a little to the observed increase in emphysema index. However, this effect is usually quite small, and we adjusted for age in the multivariate model [32]. Finally, several different makers and models of CT scanners were used. However, subjects enrolled into COPDgene study were scanned with a standardized protocol customized by scanner model [18].

In conclusion, current smokers have significantly more evidence of inflammation of the small and large airways than former smokers, and that these effects may account in part for the apparent decrease in emphysema index in current smokers.

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