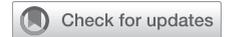# Luminal Plugging on Chest CT Scan
Association With Lung Function, Quality of Life, and COPD Clinical Phenotypes

Yuka Okajima, MD, MPH; Carolyn E. Come, MD, MPH; Pietro Nardelli, PhD; Sushil K. Sonavane, MD; Andrew Yen, MD; Hrudaya P. Nath, MD; Nina Terry, MD; Scott A. Grumley, MD; Asmaa Ahmed, MD; Seth Kligerman, MD; Kathleen Jacobs, MD; David A. Lynch, MD; Barry J. Make, MD; Edwin K. Silverman, MD, PhD; George R. Washko, MD; Raúl San José Estépar, PhD; and Alejandro A. Diaz, MD, MPH

BACKGROUND: Mucous exudates occluding the lumen of small airways are associated with reduced lung function and mortality in subjects with COPD; however, luminal plugs in large airways have not been widely studied. We aimed to examine the associations of chest CT scan-identified luminal plugging with lung function, health-related quality of life, and COPD phenotypes.

METHODS: We randomly selected 100 smokers without COPD and 400 smokers with COPD from the COPDGene Study. Luminal plugging was visually identified on inspiratory CT scans at baseline and 5-year follow-up. The relationships of luminal plugging to FEV_1, St. George's Respiratory Questionnaire (SGRQ) score, emphysema on CT scan (defined as the percentage of low attenuation area < 950 Hounsfield units [%LAA-950]), and chronic bronchitis were assessed using linear and logistic multivariable analyses.

RESULTS: Overall, 111 subjects (22%) had luminal plugging. The prevalence of luminal plugging was higher in subjects with COPD than those without COPD (25% vs 10%, respectively; $P = .001$). In subjects with COPD, luminal plugging was significantly associated with FEV_1 % predicted (estimate, −6.1; SE, 2.1; $P = .004$) and SGRQ score (estimate, 4.9; SE, 2.4; $P = .04$) in adjusted models. Although luminal plugging was associated with log %LAA-950 (estimate, 0.43; SE, 0.16; $P = .007$), its relationship with chronic bronchitis did not reach statistical significance ($P = .07$). Seventy-three percent of subjects with COPD with luminal plugging at baseline had it 5 years later.

CONCLUSIONS: In subjects with COPD, CT-identified luminal plugging is associated with airflow obstruction, worse health-related quality of life, and emphysema phenotype. This imaging feature may supplement the current clinical assessment of chronic mucus hypersecretion in COPD. CHEST 2020; 158(1):121-130

KEY WORDS: airway obstruction; COPD; CT scan; luminal; mucus; plugging; smokers

Mucus dysfunction is a central pathophysiologic feature of COPD that increases mucus production and plug formation and manifests as chronic cough and phlegm.[1] In patients with COPD, mucous exudates in small airways histologically identified in resected lung tissue were known to relate to airflow obstruction and increased mortality.[2,3]

CT scan measures of relatively large airways are well known to reflect histologic measures of small airways ($\leq$ 2 mm in diameter), the primary site of airflow obstruction in COPD.[4] A study identified luminal plugging in relatively large airways on CT scan in patients with severe asthma, and demonstrated that it was associated with reduced lung function and sputum eosinophil levels and inflammatory biomarkers.[5] Although it is thought that this imaging feature reflects mucus plugging, this remains to be proven. Consequently, we use the term luminal plugging instead of mucus plugging. Understanding the functional and clinical implications of CT scan-identified luminal plugging in large airways may help guide the development of better therapies targeting mucus dysfunction. Nevertheless, CT scan-identified luminal plugging remains to be explored in COPD. Both emphysema and chronic bronchitis are known as clinical phenotypes of COPD.[6] It is conceivable that subjects with chronic bronchitis would likely form plugs in the airways, because increased mucus production is a central feature of this disease,[7] whereas the relationship between emphysema and mucus dysfunction remains to be elucidated.

We hypothesized that CT scan-identified luminal plugging is associated with decreased lung function, worse health-related quality of life (HRQL), and COPD clinical phenotypes. Additionally, we aimed to examine changes in CT scan-identified luminal plugging at 5 years of follow-up, using data from the COPDGene Study, a well-characterized cohort of smokers with and without COPD.[8]

Methods

Study Population

We used baseline (phase 1, 2008-2011) and 5-year follow-up (phase 2, 2012-2016) data from the COPDGene study, designed to determine genetic and epidemiologic determinants of COPD.[8] Briefly, African American and non-Hispanic white current and former smokers ($\geq$ 10 pack-years of cigarette smoking) 45 to 80 years of age were recruited for this study (e-Appendix 1). Each study visit included questionnaires, spirometry, and chest CT imaging. We randomly selected 500 subjects stratified by spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage at phase 1 study visit, yielding 100 subjects without COPD and 400 subjects with COPD (100 from each GOLD stage I-IV). All subjects provided written informed consent to participate in the study. The institutional review board at each participating clinical center approved the COPDGene study, and the Partners HealthCare Research Committee (No. 2007P-000554) approved the current study.

(Dr Make), National Jewish Health, Denver, CO; and the Channing Division of Network Medicine (Dr Silverman), Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

CORRESPONDENCE TO: Yuka Okajima, MD, MPH, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115; e-mail: yokajima@mail.harvard.edu

CT Scan Assessment

The COPDGene imaging protocols have been published elsewhere.[8] Pertinent to this study is the overlapping image reconstruction of the volumetric CT scans with a submillimeter slice thickness, allowing a detailed assessment of the bronchial tree. Phase 1 and phase 2 inspiratory CT scans were independently evaluated with a window width of 1,400 and a level of -500 Hounsfield units, with readers blinded to clinical information.[9] We used a sequential reading system described in e-Appendix 1.[10] Briefly, a first reader identified and scored luminal plugging for each CT scan. All positive and 20% of negative CT scans were then rated by a second reader. CT scans with discrepant luminal plugging scores were sent to a third reader. We used a scoring system proposed by Dunican et al[5] with a modification to comply with Netter's bronchial anatomy nomenclature.[11] This latter nomenclature has 18 bronchopulmonary segments instead of 20 previously used. A luminal plug was defined as an opacity that completely occludes the lumen of an airway, regardless of the airway size or generation (Fig 1). The lung zone within 2 cm from the costal or diaphragmatic pleura was excluded because the airways in that zone are too small to ascertain a complete occlusion by luminal plugs.[5] A luminal plug score was generated for each CT scan as an aggregation of the number of bronchopulmonary segments with luminal plugging, ranging from 1 to 18. In those without luminal plugging, the score is 0. If a CT scan required more than one reading, the final luminal plug score used for analysis was an average of the scores from two or three readers. Three readings were required for discrepant CT scans. The intra- and interreader agreement for the luminal plugging score was assessed as described in e-Appendix 1. The reader also visually assessed bronchiectasis[12] as detailed in e-Appendix 1. Quantitative CT measurements of lung volume, emphysema, and airways were performed with Thirona software (Thirona) (e-Appendix 1).

Spirometry

Spirometric measures of lung function were performed before and after the administration of albuterol following the American Thoracic Society[13] recommendations. Postbronchodilator FEV_1 and FVC are
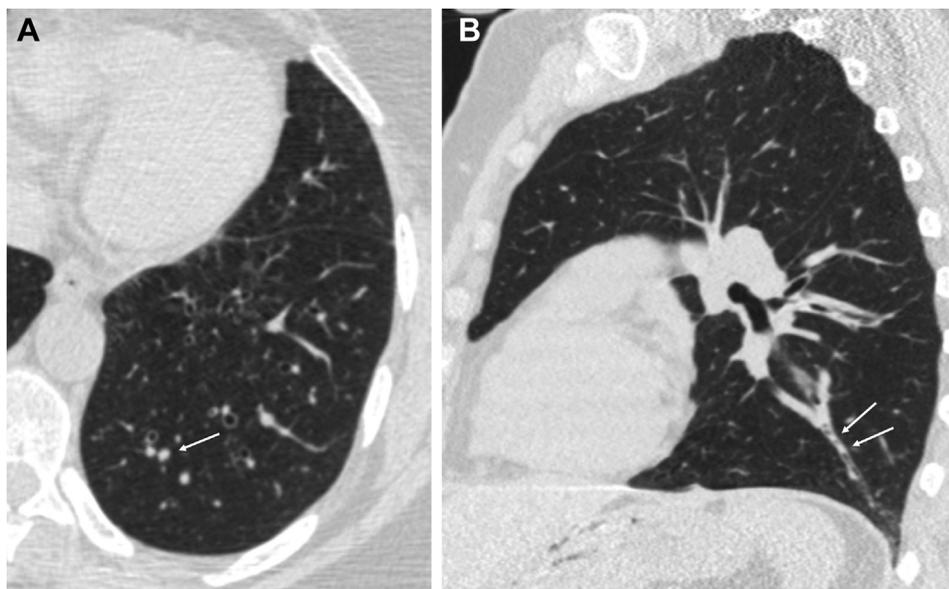
Figure 1 – A-B, CT scan findings of luminal plugging. (A) An axial image shows a luminal plug as a round opacity occluding the lumen of a branch of the left posterior basal bronchopulmonary segment (arrow). (B) The sagittal image shows luminal plugs as tubular opacities within the same airway (arrows).

expressed as % predicted values.[14] COPD was defined as $FEV_1/FVC <$ 0.7, and its severity was classified based on spirometric GOLD stages I through IV.[15] We used forced expiratory flow at 25% to 75% of the FVC ($FEF_{25\%-75\%}$) (L/s) as a functional measure reflecting small airway disease. Bronchodilator reversibility was defined as at least 12% and 200-mL increase in FEV_1 or FVC, or both.[16]

Clinical Assessment

Demographic and clinical data were collected with standardized questionnaires (available at www.COPDGene.org).[8] HRQL was assessed using the St. George's Respiratory Questionnaire (SGRQ) total score, ranging from 0 to 100; a higher score indicates worse HRQL.[17] A subject was considered to have a cough and phlegm if he/she had coughed and brought up phlegm almost every day or most days a week over the last 4 weeks, respectively, based on the SGRQ. A subject was considered to have dyspnea if he/she had a modified Medical Research Council score of $\geq$ 1.[18] Chronic bronchitis was considered present if a subject had chronic cough and phlegm production for $\geq$ 3 months per year for at least 2 consecutive years.[19] A subject was considered to have asthma if he/she reported a current physician diagnosis of asthma.

Statistical Analysis

Differences between subjects with and without luminal plugging at phase 1 visit were compared using the Fisher exact test and the Student t test as appropriate. Because most subjects with luminal plugging had it in one or two bronchopulmonary segments, we report the primary analyses using luminal plugging as a binary variable (presence/absence). Multivariate analyses were performed using linear and logistic regression models for binary and continuous variables, where appropriate. Model building was performed a priori. The main models for FEV_1 % predicted, $FEF_{25\%-75\%}$ SGRQ, chronic bronchitis, and respiratory symptoms included age, sex, race, BMI, current smoking status, pack-years of smoking history, current asthma, bronchiectasis, and CT scan measures of emphysema and airway wall thickness. The models for emphysema on CT scan (ie, as continuous percentage of low attenuation area < -950 Hounsfield units [%LAA-950] and binary variable defined as %LAA-950 $\geq$ 5%),[20] were adjusted for the same above variables but %LAA-950. Secondary models for all those outcomes but spirometric measures of lung function included FEV_1 as a covariate. $FEF_{25\%-75\%}$ and % LAA-950 were log-transformed because they were not normally distributed. $P < .05$ was considered statistically significant. Analyses were conducted with SAS 9.4 software (SAS Institute) and STATA 14 (StataCorp LLC).

Results

The intra- and interreader agreement results and a Bland-Altman plot (e-Fig 1) are shown in e-Appendix 1.

Luminal Plugging at Phase 1

Out of the 500 subjects, 111 (22%) had luminal plugging. Subjects with COPD were more likely to have luminal plugging than subjects without COPD (25% vs 10%, respectively; $P = .001$), and the prevalence of subjects with luminal plugging increased with GOLD stage

(Fig 2). Luminal plugs were mostly found in the lower lobes among subjects with COPD (78%) (e-Fig 2). Overall, the median luminal plug score was 1.5 (range, 1-11). The median luminal plug score across spirometric GOLD stages I through IV was 1 (range, 1-3), 1 (range, 1-11), 2 (range, 1-9), and 2 (range, 1-8), respectively. The distribution of the luminal plug score among all subjects is shown in Figure 3.

Overall, compared with subjects without luminal plugging, subjects with luminal plugging were older and
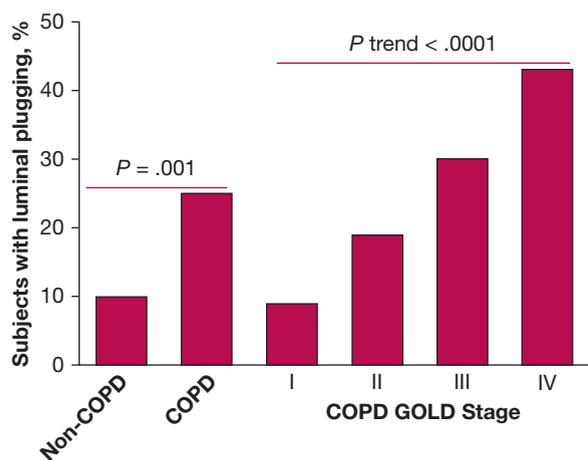
Figure 2 – *The percentage of subjects with luminal plugging at phase 1 of the COPDGene Study. The bars represent the percentage of subjects with luminal plugging in those without COPD and those with COPD by spirometric GOLD stage. Note that the percentage of subjects with luminal plugging increased with the spirometric GOLD stage. The percentage for each bar was calculated using 100 study subjects for the non-COPD group and each GOLD stage except for overall subjects with COPD, where it was calculated with 400. GOLD = Global Initiative for Chronic Obstructive Lung Disease.*

more likely to have phlegm and dyspnea (Table 1). These subjects with luminal plugging have higher SGRQ total scores (worse HRQL); lower FEV$_1$ % predicted, FVC % predicted, FEV$_1$/FVC ratio, and FEF$_{25\%-75\%}$; and greater CT scan measures of emphysema, air trapping, and airway wall thickness than those without plugging (Fig 4, Table 1).

Characteristics of the subjects with and without COPD and by luminal plugging status and by GOLD stage are shown in e-Tables 1 and 2. The prevalence of luminal plugging among subjects with COPD with asthma, chronic bronchitis, or bronchiectasis was higher than those without these conditions (37% vs 23%, P = .04;

34% vs 22%, P = .02; 36% vs 20%, P = .001, respectively). When asthma is excluded, the prevalence of luminal plugging among subjects with COPD (n = 340) was 23%. The prevalence of luminal plugging was higher in subjects with bronchodilator reversibility (n = 133) than those without bronchodilator reversibility (32% vs 22%, respectively; P = .012). Those having one or more COPD exacerbations in the previous year had a nonsignificant trend of a higher prevalence of luminal plugging than those who reported no exacerbation (30% vs 23%, respectively; P = .09). There were no differences in luminal plugging prevalence between current and former smokers with COPD (P = .64).

Associations of Luminal Plugging With Lung Function and SGRQ in Subjects With COPD

CT scan-identified luminal plugging was significantly associated with FEV$_1$ % predicted (estimate, −6.1%; SE, 2.1%; P = .004) in adjusted models. The association between CT scan-identified luminal plugging and FEF$_{25\%-75\%}$ (log-transformed estimate, −0.11; SE, 0.06 L/s, P = .08) did not reach statistical significance. The robust association between luminal plugging and FEV$_1$ suggests that luminal plugging is in the causal line of lung function impairment. Therefore, in subsequent main models for SGRQ, COPD phenotypes, and respiratory symptoms, we did not use FEV$_1$ as a covariate to allow assessing the potential relationship of a modifiable feature (ie, luminal plugging) and those outcomes, regardless of disease severity. For completeness, secondary models with FEV$_1$ as covariate are also shown. After adjustment for the same covariates used for the FEV$_1$ model, luminal plugging was associated with SGRQ (estimate, 4.9; SE, 2.4; P = .04)
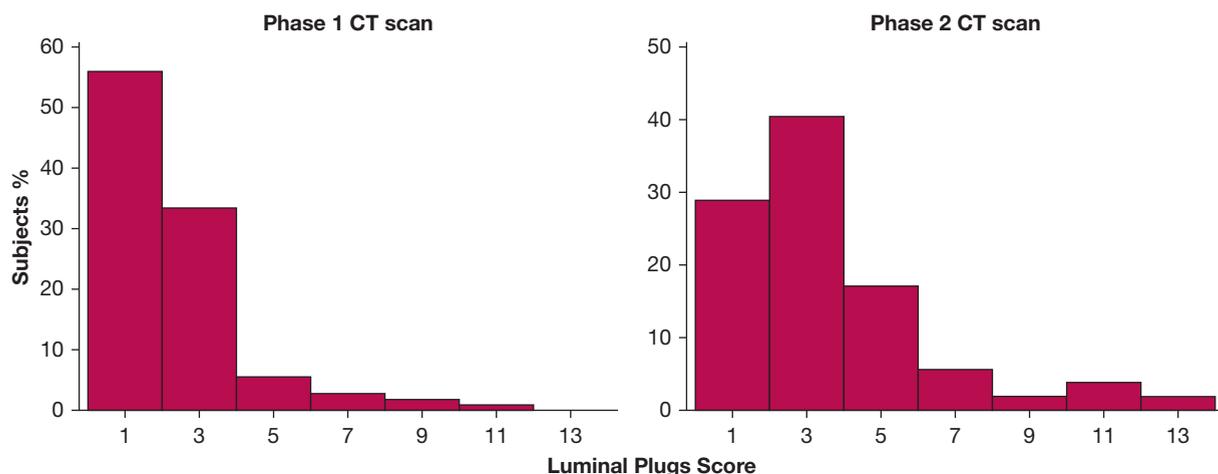

Figure 3 – *Distribution of CT scan-identified luminal plug scores at phases 1 (n = 111) and 2 (n = 52) of the COPDGene Study. Subjects without luminal plugging were not included.*

TABLE 1] All Subjects' Baseline Characteristics by CT Scan-Identified Luminal Plugging Status

Characteristics	Subjects Without Luminal Plugging (n = 389)	Subjects With Luminal Plugging (n = 111)	P Value
Age, y	62 ± 9	65 ± 8	.0002
Female	57	54	.59
African American race	29	22	.12
BMI, kg/m^2	28 ± 6	26 ± 6	.0007
Current smoking status, yes	45	41	.39
Pack-years smoked	46 ± 23	55 ± 35	.002
Cough	47	58	.053
Phlegm	39	55	.002
Dyspnea	57	81	< .0001
Asthma	11	20	.03
Chronic bronchitis	22	35	.006
Bronchiectasis on CT scan	28	50	< .0001
SGRQ total score	30 ± 24	44 ± 23	< .0001
FEV$_1$ % predicted[a]	68 ± 29	46 ± 26	< .0001
FVC % predicted[a]	87 ± 21	74 ± 19	< .0001
FEV$_1$/FVC, %[a]	58 ± 17	45 ± 17	< .0001
FEF$_{25\%-75\%}$, L/sec[a]	1.2 ± 1.1	0.6 ± 0.8	< .0001
TLC$_{CT}$ % predicted	99 ± 17	106 ± 15	.0002
%LAA-950	9 ± 12	17 ± 14	< .0001
%LAA-856	28.7 ± 21	46 ± 21	< .0001
Pi10, mm^2	2.5 ± 0.6	2.8 ± 0.6	< .0001

Values are mean ± SD, %, or as otherwise indicated. Missing data: TLC$_{CT}$, %LAA-950, and Pi10, 24 each; %LAA-856, 83. FEF$_{25\%-75\%}$ = forced expiratory flow at 25% to 75% of the FVC; %LAA-856 = percentage of low attenuation areas < −856 Housfield units; %LAA-950 = percentage of low attenuation area < −950 Hounsfield units; Pi10 = the wall area of a theoretical airway of 10 mm luminal perimeter; SGRQ = St. George's Respiratory Questionnaire. TLCCT = CT measure of total lung capacity.
[a]Postbronchodilator pulmonary function measurements are presented.

(Table 2). The association between luminal plugging and SGRQ was not statistically significant when FEV$_1$ was added to the model (P = .26).

Association of Luminal Plugging With Emphysema and Chronic Bronchitis Phenotypes and Respiratory Symptoms in Subjects With COPD

Emphysema, defined as %LAA-950 ≥ 5% on CT scan, was present in 60% of the subjects with COPD. Luminal plugging was more prevalent in those with emphysema than those without emphysema (33% vs 13%, respectively; P < .0001). Based on emphysema and luminal plugging statuses, subjects were grouped into 4 groups and their characteristics are shown in e-Table 3. In a multivariable model, luminal plugging was related to the emphysema phenotype as continuous (estimate, 0.43; SE, 0.16) and binary (OR, 2.06; 95% CI, 1.09-3.90) variable (Table 3). Chronic bronchitis was present in 112 subjects with COPD (28%), and the prevalence of luminal plugging was higher in those with COPD and

chronic bronchitis than those with COPD alone (34% vs 22%, respectively; P = .02). In a multivariable model, luminal plugging tended to increase the odds of chronic bronchitis, but the relationship did not reach statistical significance (OR, 1.68; 95% CI, 0.95-2.97; P = .07) (Table 3). Luminal plugging was related to dyspnea but not to phlegm in the main multivariable models (e-Table 4).

Luminal Plugging at Phase 2

Out of 500 subjects, 287 returned to phase 2 study visit 5 years later, whereas 113 were deceased, and 100 were lost to follow-up. Phase 2 CT scan data were available on 238 subjects, including 178 subjects with COPD and 60 subjects without COPD. Luminal plugging was found in 52 subjects, with a higher prevalence in those with COPD than those without COPD (28% vs 5%, respectively). The distribution of luminal plug scores among all subjects is shown in Figure 3, and the changes in luminal plugging status from phase 1 CT scan to
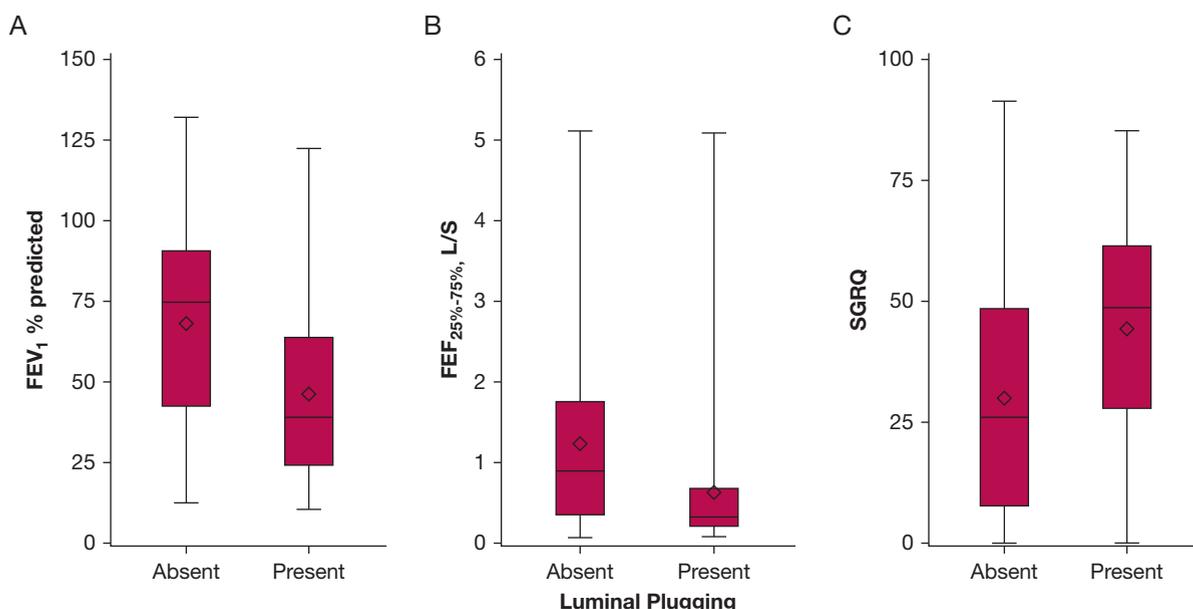
Figure 4 – *(A) FEV$_1$ % predicted, (B) FEF$_{25\%-75\%}$, and (C) SGRQ total score among subjects with COPD by luminal plug status at phase 1. The box plots show the median (horizontal line in the middle of the box), mean (diamond), and 25th and 75th percentiles (bottom and top lines of the box) of FEV$_1$ % predicted, FEF$_{25\%-75\%}$, and SGRQ total score. The whiskers represent the upper and lower values (1.5 times above the 75th percentile and below the 25th percentile, respectively). P < .0001 for the difference in FEV$_1$ % predicted, FEF$_{25\%-75\%}$, and SGRQ between those with and without luminal plugging in univariate analysis. See text for details in adjusted models for these outcomes. FEF$_{25\%-75\%}$ = forced expiratory flow at 25% to 75% of the FVC; SGRQ = St. George's Respiratory Questionnaire.*

phase 2 CT scan is shown in Figure 5. In subjects with COPD, luminal plugs on phase 2 CT scan were also most frequently (82%) found in the lower lobes (Fig 2). Among subjects with COPD with luminal plugging at phase 1 (n = 30), 22 subjects (73%) had and 8 (27%) did not have luminal plugging at phase 2. Out of 148 subjects with COPD without luminal plugging at phase 1, 18% had luminal plugging at phase 2.

Discussion

We identified luminal plugging in relatively large intraparenchymal airways on chest CT scans from 500 current and former smokers with and without COPD, and found that the prevalence of luminal plugging was higher in subjects with COPD (vs non-COPD) and increased with spirometric GOLD stage. In COPD, luminal plugging is associated with decreased lung function, worse HRQL, and the emphysema phenotype. Furthermore, 73% of subjects with COPD with luminal

plugging at baseline had this abnormality at 5-year follow-up. This study provides novel information on CT scan-identified luminal plugging and its change over time in COPD.

Increased mucus production, impaired mucociliary clearance, and more viscous mucus lead to plug formation in subjects with COPD.[21] We found that 25% of subjects with COPD surveyed had luminal plugging, which was less prevalent than that reported in patients with asthma (58%-67%).[5,22] The prevalence of subjects with luminal plugging increased with disease severity of COPD. This finding is similar to that reported in a lung tissue study where the extent of mucous exudates in the lumen of small airways increased with spirometric GOLD stage.[3]

In our study, CT scan-identified luminal plugging was associated with lower FEV$_1$ % predicted, independently of overlapping asthma, bronchiectasis, and CT scan

TABLE 2] Multivariable Analyses for the Associations Between CT Scan-Identified Luminal Plugging at Phase 1 and Spirometric Measures of Lung Function and SGRQ in Subjects With COPD

Luminal Plugging	FEV$_1$ % Predicted	Log FEF$_{25\%-75\%}$ (L/s)	SGRQ
Absent	Ref	Ref	Ref
Present	−6.1 (2.1), .004	−0.11 (0.06), .08	4.9 (2.4), .04

Values are estimate (SE), P value. All models were adjusted for age, sex, race, BMI, current smoking status, smoking pack-years history, asthma, CT scan-identified bronchiectasis, and CT measures of emphysema and airway wall thickness. All analyses were the results from multivariable linear regression models. Ref = reference. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Multivariable Analyses for the Associations of CT Scan-Identified Luminal Plugging at Phase 1 With Emphysema and Chronic Bronchitis in Subjects With COPD

Model		Log Emphysema on CT Scan	Emphysema ≥ 5% on CT Scan (Yes/No)	Chronic Bronchitis
Model 1				
Luminal plugging	Absent	Ref	Ref	Ref
	Present	0.43 (0.16), .007	2.06 (1.09-3.90), .02	1.68 (0.95-2.97), .07
Model 2				
Luminal plugging	Absent	Ref	Ref	Ref
		0.21 (0.14), .14	1.52 (0.76-3.07), .24	1.55 (0.87-2.76), .14

Values are estimate (SE), *P* value or OR (95% CI), *P* value. Model 1 for chronic bronchitis was adjusted for age, sex, race, BMI, current smoking status, smoking pack-years history, asthma, CT scan-identified bronchiectasis, and CT scan measures of emphysema and airway wall thickness. The same covariates were used in the model for emphysema on CT scan but log-transformed %LAA-950. Model 2 has all model 1 covariates and FEV$_1$. See Table 1 and 2 legends for expansion of abbreviations.

measures of emphysema and airway wall thickness. These findings are consistent with previous studies on patients with asthma, which reported a 25% decrease in FEV$_1$ % predicted in those with high luminal plug score (≥ 4) compared with those without plugging, and that luminal plugging was associated with ventilation heterogeneity on MRI.[5,22] Although our study cannot explain the mechanisms underlying these associations, possibilities include the following: (1) complete obstruction of the airways by luminal plugging leading to a regional or more widespread airflow limitation; (2) differing susceptibility to developing luminal plugging among subjects with severe vs mild COPD; and (3) COPD exacerbations, which are associated with luminal plugging, leading to loss of lung function. Further longitudinal studies are warranted to understand our
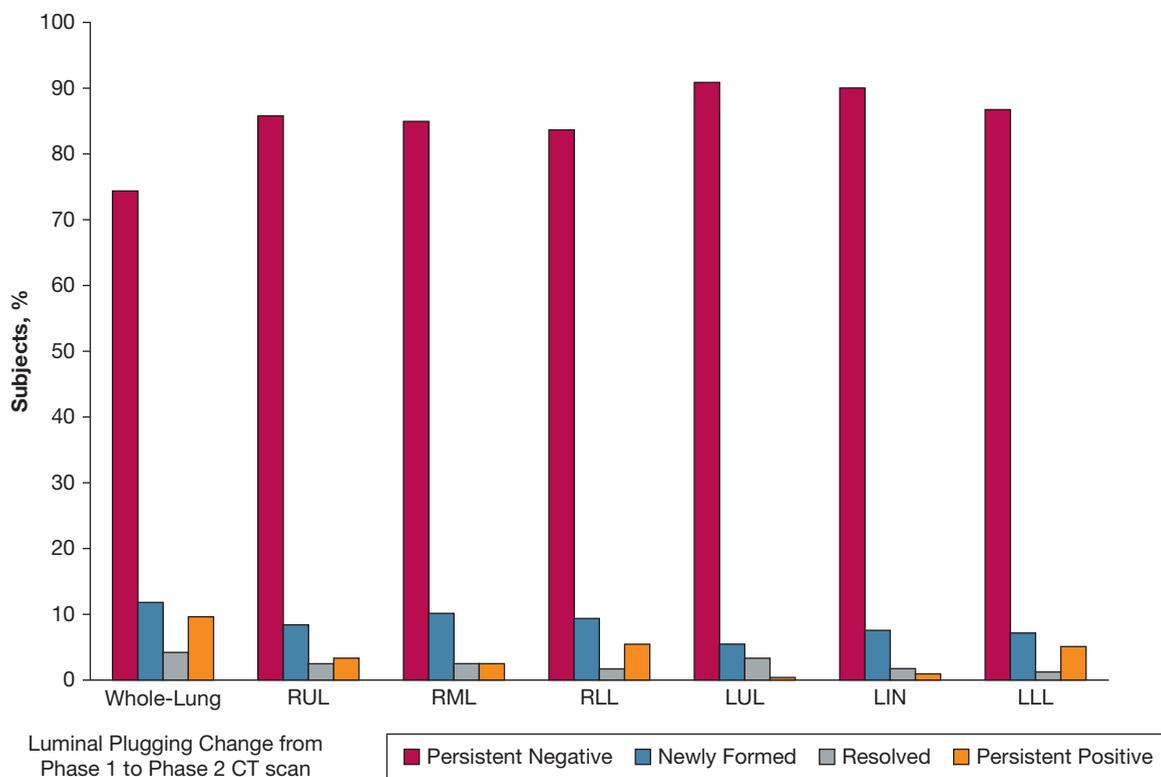

Figure 5 – Five-year changes in luminal plugging presence for the whole lung and by lobe in all study subjects with both phase 1 and phase 2 CT scans available (n = 238). The bars show the percentage of subjects by group as follows: persistent negative (no luminal plugging on phase 1 and 2 CT scans); persistent positive (luminal plugging on phase 1 and 2 CT scans); newly formed (no luminal plugging on phase 1 CT scan and luminal plugging on phase 2 CT scan); and resolved (luminal plugging on phase 1 CT scan and no luminal plugging on phase 2 CT scan). LIN = lingula; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

observations better. Most subjects had lower lobe predominant luminal plugging. One explanation for this finding is gravity, which may make more mucus pooling in the lower lobe airways than upper lobe airways.

A novel finding in this study was that luminal plugging was directly associated with the emphysema phenotype of COPD, both when used as a continuous and binary variable. We are not aware of any other studies reporting this association. The association we observed does not prove causality; possible explanations for this relationship are as follows. First, subjects with COPD with luminal plugging have an increased inflammatory burden that may independently contribute to or facilitate lung parenchyma damage. In severe asthma, higher IL-5 and IL-13 concentrations in sputum cells were associated with high mucus plugs on CT scan, and IL-5 blood levels are higher in subjects with COPD with emphysema vs without emphysema.[23] Second, subjects with COPD with emphysema might be prone to develop luminal plugging because of loss of airway tethering. Airways without tethering tend to collapse, and their lumen narrows.[24] For a given amount of mucus, a collapsible airway may tend to form plugs more easily than a noncollapsible airway. In our main models for emphysema, we did not use FEV_1 as a covariate based on the robust relationship between luminal plugging and airflow; and our goal was to examine this imaging feature, which might be amenable for therapeutic intervention as in other diseases, such as cystic fibrosis, regardless of the severity of airflow limitation.[25]

In contrast to the luminal plugging-emphysema relationship observed, we found luminal plugging was not related to chronic bronchitis or cough and phlegm. This finding is in agreement with a study on patients with COPD reporting a lack of relationship between luminal plugs in small airways and symptoms of cough and phlegm.[3] Another study also failed to demonstrate an association between luminal plugging on CT scan and cough and phlegm in severe asthma.[5] A possibility to explain this lack of association is that the airways where plugs form may have fewer cough receptors.[5] We also found that 30% of subjects with COPD with CT scan-identified luminal plugging reported neither cough nor phlegm, suggesting that the identification of chronic mucus hypersecretion should not rely only on symptoms and that CT scan may provide a unique phenotype for mucus dysfunction.

Another interesting finding was that subjects with CT scan-identified luminal plugging (vs those without luminal plugging) had a thicker airway wall as measured by the wall area of a theoretical airway of 10 mm luminal perimeter. This wall thickening may reflect the remodeling that occurs in subjects susceptible to forming intraluminal plugs in large airways in a similar manner to what was described in small airways. Hogg et al[2] demonstrated that in addition to mucous exudates occluding the lumen of small airways, the walls were also thickened. We also found that the prevalence of luminal plugging was higher in subjects with bronchodilator reversibility than those who did not have that response. Subjects with asthma and COPD (vs COPD alone) had a higher prevalence of luminal plugging as well. Because bronchodilator reversibility is used to diagnose asthma, these findings are consistent with the high prevalence of mucus plugging reported in asthma studies. Further studies are needed to understand the potential clinical impact of luminal plugging in subjects with asthma-COPD overlap.

In this study, we also found that subjects with luminal plugging on CT scan had worse HRQL than those without plug formation. The difference in SGRQ total score was not only statistically significant but clinically meaningful (> 4 points). This finding expands prior studies in COPD linking CT scan measures of emphysema and airway wall thickness with HRQL,[25] an outcome used in ongoing clinical trials in smokers.[26]

The assessment of 5-year follow-up CT images provides novel insight into temporal changes in CT scan-identified luminal plugging in COPD. Seventy-three percent of subjects with COPD with luminal plugging at phase 1 had this imaging feature in phase 2, suggesting that a subgroup of subjects tends to be persistent producers of mucus plugs. Although our study does not address the underlying mechanism of mucus plug formation, it has been suggested to be a result of elevated type 2 inflammation as seen in severe asthma.[5]

This study has several limitations. First, we used a cohort of heavy smokers with and without COPD, and in our study design, severe and very severe COPD is overrepresented. Although this might not represent the full spectrum of smokers, our sampling did include the full spectrum of COPD stages. Second, although our findings lack histologic validations, our main results were consistent with those from the previous lung tissue studies in COPD.[2,3] Third, we used luminal plugging as a binary variable, not the score, for our primary analyses. Moreover, although our score slightly differed from that

used in asthma studies making the scores not directly comparable, we found similar findings to the previous asthma study that used a three-category luminal plug score.[5] We think the validation and clinical utility of a luminal plug score in subjects with COPD deserves further study. Finally, although the number of subjects with phase 2 CT scans available was relatively low, limiting our ability to assess the clinical impact of luminal plugging over time, we did provide novel data on this imaging feature in COPD at two points in time. Further large longitudinal studies may be warranted.

In summary, CT scan-identified luminal plugging is frequent in subjects with COPD and related to disease severity, worse HRQL, and emphysema phenotype of COPD. CT imaging might be a useful tool to assess luminal plugging and potentially to evaluate novel therapies targeting mucus dysfunction.

References

1. Burgel PR, Martin C. Mucus hypersecretion in COPD: Should we only rely on symptoms? *Eur Respir Rev*. 2010;19(116):94-96.

2. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645-2653.

3. Hogg JC, Chu FS, Tan WC, et al. Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *Am J Respir Crit Care Med*. 2007;176(5):454-459.

4. Nakano Y, Wong JC, de Jong PA, et al. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med*. 2005;171(2):142-146.

5. Dunican EM, Elicker BM, Gierada DS, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018;128(3):997-1009.

6. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(3):228-237.

7. Kesimer M, Ford AA, Ceppe A, et al. Airway mucin concentration as a marker of chronic bronchitis. *N Engl J Med*. 2017;377(10):911-922.

8. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *Copd*. 2010;7(1):32-43.

9. Bankier AA, Fleischmann D, Mallek R, et al. Bronchial wall thickness: appropriate window settings for thin-section CT and radiologic-anatomic correlation. *Radiology*. 1996;199(3):831-836.

10. Washko GR, Lynch DA, Matsuoka S, et al. Identification of early interstitial lung disease in smokers from the COPDGene Study. *Acad Radiol*. 2010;17(1):48-53.

11. Netter F. *Atlas of Human Anatomy*. Summit, NJ: Medical Education and Publishing, Ciba-Geigy Corporation; 1989.

12. Diaz AA, Young TP, Maselli DJ, et al. Quantitative CT measures of bronchiectasis in smokers. *Chest*. 2017;151(6):1255-1262.

13. Standardization of spirometry, 1994 update. American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152(3):1107-1136.

14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179-187.

15. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD

executive summary. *Am J Respir Crit Care Med*. 2013;187(4):347-365.

16. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948-968.

17. Diaz AA, Petersen H, Meek P, Sood A, Celli B, Tesfaigzi Y. Differences in health-related quality of life between New Mexican Hispanic and non-Hispanic white smokers. *Chest*. 2016;150(4):869-876.

18. Diaz AA, Valim C, Yamashiro T, et al. Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers. *Chest*. 2010;138(4):880-887.

19. Kim V, Crapo J, Zhao H, et al. Comparison between an alternative and the classic definition of chronic bronchitis in COPDGene. *Ann Am Thorac Soc*. 2015;12(3):332-339.

20. Han MK, Tayob N, Murray S, et al. Association between emphysema and chronic obstructive pulmonary disease outcomes in the COPDGene and SPIROMICS cohorts: a post hoc analysis of two clinical trials. *Am J Respir Crit Care Med*. 2018;198(2):265-267.

21. Kim V, Evans CM, Dickey BF. Dawn of a new era in the diagnosis and treatment of airway mucus dysfunction. *Am J Respir Crit Care Med*. 2019;199(2):133-134.

22. Svenningsen S, Haider E, Boylan C, et al. CT and functional MRI to evaluate airway mucus in severe asthma. *Chest*. 2019;155(6):1178-1189.

23. Nakamura M, Nakamura H, Minematsu N, et al. Plasma cytokine profiles related to smoking-sensitivity and phenotypes of chronic obstructive pulmonary disease. *Biomarkers*. 2014;19(5):368-377.

24. Diaz AA, Han MK, Come CE, et al. Effect of emphysema on CT scan measures of airway dimensions in smokers. *Chest*. 2013;143(3):687-693.

25. Martinez CH, Chen YH, Westgate PM, et al. Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. *Thorax*. 2012;67(5):399-406.

26. University of Michigan and National Heart, Lung, and Blood Institute. RETHINC: REdefining THerapy In Early COPD for the Pulmonary Trials Cooperative. NCT02867761. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2007. https://clinicaltrials.gov/ct2/show/NCT02867761. Updated July 26, 2019.