Association between Functional Small Airway Disease and FEV_1 Decline in Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: The small conducting airways are the major site of airflow obstruction in chronic obstructive pulmonary disease and may precede emphysema development.

Objectives: We hypothesized a novel computed tomography (CT) biomarker of small airway disease predicts FEV_1 decline.

Methods: We analyzed 1,508 current and former smokers from COPDGene with linear regression to assess predictors of change in FEV_1 (ml/yr) over 5 years. Separate models for subjects without and with airflow obstruction were generated using baseline clinical and physiologic predictors in addition to two novel CT metrics created by parametric response mapping (PRM), a technique pairing inspiratory and expiratory CT images to define emphysema (PRM^{emph}) and functional small airways disease (PRM^{fSAD}), a measure of nonemphysematous air trapping.

Measurements and Main Results: Mean (SD) rate of FEV_1 decline in ml/yr for GOLD (Global Initiative for Chronic Obstructive Lung Disease) 0–4 was as follows: 41.8 (47.7), 53.8 (57.1), 45.6 (61.1), 31.6 (43.6), and 5.1 (35.8), respectively (trend test for grades 1–4; $P < 0.001$). In multivariable linear regression, for participants without airflow obstruction, PRM^{fSAD} but not PRM^{emph} was associated with FEV_1 decline ($P < 0.001$). In GOLD 1–4 participants, both PRM^{fSAD} and PRM^{emph} were associated with FEV_1 decline ($P < 0.001$ and $P = 0.001$, respectively). Based on the model, the proportional contribution of the two CT metrics to FEV_1 decline, relative to each other, was 87% versus 13% and 68% versus 32% for PRM^{fSAD} and PRM^{emph} in GOLD 1/2 and 3/4, respectively.

Conclusions: CT-assessed functional small airway disease and emphysema are associated with FEV_1 decline, but the association with functional small airway disease has greatest importance in mild-to-moderate stage chronic obstructive pulmonary disease where the rate of FEV_1 decline is the greatest.

Clinical trial registered with www.clinicaltrials.gov (NCT 00608764).

Keywords: FEV_1; lung function; parametric response mapping

At a Glance Commentary

Scientific Knowledge on the Subject: Airflow obstruction is influenced by both small airway disease and emphysema. The small conducting airways are the major site of airflow obstruction in chronic obstructive pulmonary disease, and histologic data suggest small airway abnormality may precede emphysema. The impact of these components of chronic obstructive pulmonary disease on lung function decline remains unknown.

What This Study Adds to the Field: In a population of current and former smokers, we demonstrate that the rate of FEV_1 decline is greatest in mild chronic obstructive pulmonary disease. A novel, computed tomography biomarker demonstrates functional small airway disease contributes to lung function decline particularly in mild disease, even among individuals without airflow obstruction.

Cigarette smoking is associated with an accelerated decline in FEV_1, resulting in airflow obstruction in a significant proportion of smokers (1). FEV_1 is influenced by both airway resistance and reduced elastic recoil caused by emphysema (2). The small conducting airways less than 2 mm in diameter that offer little resistance to airflow in normal lungs become the major site of airflow obstruction in persons with chronic obstructive pulmonary disease (COPD) (3, 4), representing a "silent zone" within the lung where obstructive airway disease can accumulate without being noticed (3–5). In fact, histologic and micro computed tomography (CT) data from explanted lung tissue suggest that widespread narrowing and destruction of the smaller airways actually occurs before emphysematous lesions become large enough to be visible on standard CT imaging (6). Unfortunately, the resolution of current clinical CT imaging prevents direct visualization of small airways disease beyond the subsegmental bronchi.

Although small airways disease can be assessed by "gas trapping," defined as the percent of voxels less than −856 Hounsfield units (HU) on expiratory CT, a significant limitation of this approach is that many lung regions that trap gas on exhalation also show emphysematous destruction when fully inflated to total lung capacity (TLC) (7). A recently developed CT analytic method, parametric response mapping (PRM), matches inspiratory and expiratory images on a voxel-by-voxel basis to examine the change in density between inspiratory and expiratory images (8). By applying separate density thresholds to the inspiratory and expiratory voxel measurements, we are able to discriminate emphysema (PRM^{emph}) from nonemphysematous air trapping, termed functional small airways disease (PRM^{fSAD}) (Figure 1; *see* Figure E1 in the online supplement).

Although emphysema defined as the percent of voxels less than −950 HU on inspiratory CT has previously been associated with lung function decline, the relative contribution of CT-defined small airways disease has not been examined (9). Here we present an analysis of a large multicenter study of current and former smokers to understand the relative contribution of small airways disease and emphysema to subsequent lung function decline across the disease severity spectrum over a 5-year period of observation. Some of the results in this study have been previously reported in the form of an abstract (10).

Methods

Study Population and Assessments

Subjects participating in the follow-up phase of COPDGene (Genetic Epidemiology of COPD), a large multicenter longitudinal observational cohort study, were included in this analysis. Written informed consent was obtained from each subject and the study was approved by the institutional review boards of all 21 participating centers. Current and former smokers with greater than or equal to 10 pack-year smoking history, with and without airflow obstruction, were enrolled (11). Inclusion criteria also included non-Hispanic white or African American race; exclusion criteria included a history of other lung disease except asthma, prior surgical excision

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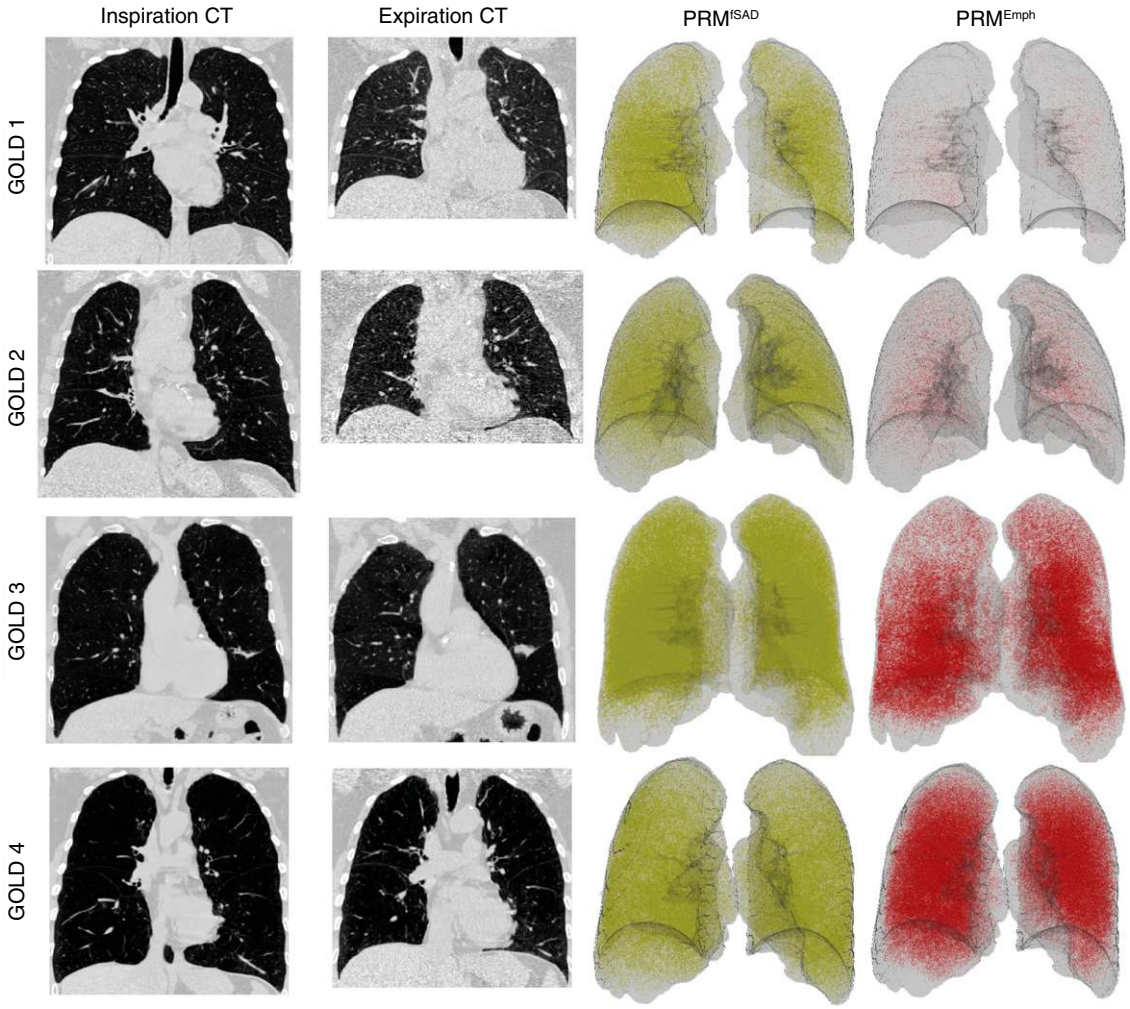

	PRM Normal (%)	PRM Functional Small Airways Disease (%)	PRM Emphysema (%)
GOLD 1	78.8	18.5	0.8
GOLD 2	44.9	41.6	7.0
GOLD 3	28.8	40.8	25.1
GOLD 4	21.8	26.9	43.2

Figure 1. Graphic representation of the parametric response mapping (PRM) methodology. Chronic obstructive pulmonary disease of GOLD (Global Initiative for Chronic Obstructive Lung Disease) grades 1–4 are shown in *rows*. Inspiratory and expiratory computed tomography (CT) images, respectively, are shown on the *left*. PRM emphysema (PRM^{Emph}) voxels in *red* and PRM functional small airways (PRM^{fSAD}) voxels in *yellow* are shown on the *right*. Although every voxel receives an individual categorical assignment, in this example PRM^{Emph} and PRM^{fSAD} are distributed throughout the lung. Greater intensity of color indicates more voxels classified in each category.

involving a lung lobe or greater, active cancer, metal in the chest, and history of chest radiation therapy. The original COPDGene cohort enrolled 10,192 individuals. A total of 1,508 GOLD (Global Initiative for Chronic Obstructive Lung Disease) 0–4 subjects who had completed a second COPDGene visit approximately 5 years after the first visit with acceptable pulmonary function and CT scans from visit 1 and 2 by November 2014 were included for this analysis (*see* Figure E2).

At both visits, spirometry was performed before and after administration of 180 μg of albuterol (Easy-One spirometer; NDD, Andover, MA). Bronchodilator reversibility was defined as at least 12% and 200 ml increase in FEV_1 and/or FVC post-bronchodilator (12); post-bronchodilator values were used for analyses (12). COPD was defined by post-bronchodilator FEV_1/FVC less than 0.70 at baseline visit per the GOLD guidelines (13). Disease severity was defined by GOLD grade. GOLD 0 was defined as by post-bronchodilator FEV_1/FVC greater than or equal to 0.70 at baseline visit and FEV_1% predicted greater than or equal to 80. Participants with FEV_1/FVC greater than 0.70 but with FEV_1 greater than 80%

predicted were deemed to have preserved ratio impaired spirometry and were not included in the analyses (14).

Data on demographics, smoking burden, respiratory morbidity, exacerbations, and comorbidities used in this analysis were recorded at the baseline visit. Respiratory disease-related health impairment and quality of life was assessed using the St. George's Respiratory Questionnaire (15), and dyspnea using the Modified Medical Research Council dyspnea score (16). History of exacerbations in the previous year was obtained at the time of initial visit, with exacerbations defined as acute worsening of respiratory symptoms that required use of either antibiotics or systemic steroids (13).

At the baseline visit, paired inspiratory and expiratory scans were obtained at maximal inspiration (TLC) and end-tidal expiration (FRC) (11). Emphysema was quantitated using the percentage of low-attenuation units less than −950 HU at TLC, and gas trapping using the percentage of low-attenuation units less than −856 HU at end-expiration using Slicer software (www.Slicer.org) (17). Using funds from NHLBI (grant R01 HL122438), PRM analysis was also performed on paired registered inspiratory and expiratory images to distinguish functional small airways disease (PRM^{fSAD}) from emphysema (PRM^{emph}) by Imbio LLC (Minneapolis, MN) using lung density analysis software (8). Briefly, PRM^{fSAD} was defined as areas of lung that are greater than −950 HU on inspiration but also less than −856 HU on expiration. PRM^{emph} was defined as areas of lung that are less than −950 HU on inspiration and less than −856 HU on expiration (*see* Figure E1).

Statistical Analyses

All statistical analyses were performed in SAS version 9.3 (Cary, NC). Comparisons were performed using two-sample *t* tests for continuous variables and chi-square statistics for categorical variables. Linear regression was used to study univariate and multivariable associations between potential predictors and change in FEV_1 (ml/yr). The outcome of change in FEV_1 for each individual was calculated by subtracting visit 1 FEV_1 from visit 2 FEV_1 and dividing by the time between visits to calculate change in ml/yr. In addition to PRM CT metrics, which were the covariates of interest, age, sex, race, height, smoking history, and scanner type were included as covariates in all multivariable regression models regardless of univariate statistical significance. Otherwise, only parameters associated with FEV_1 change at a significance level of *P* less than 0.05 were retained in the multivariable model. Linear regression analyses were repeated separately for GOLD 0 participants and also for GOLD 1–4 participants. Among GOLD 1–4 participants, the contribution to FEV_1 decline for each CT metric was calculated by multiplying the parameter estimate from the multivariable model by the mean CT metric value for the corresponding disease stage and dividing that value by the sum of this product for both metrics (PRM^{fSAD} and PRM^{emph}). *P* less than 0.05 was considered statistically significant for all analyses.

Results

Subject Characteristics

Results for 1,508 participants with complete data needed for multivariable regression analyses are reported here (*see* Figure E2). Baseline demographics and lung function are reported in Table 1, categorized by severity of airflow obstruction according to GOLD grade. Imaging metrics show an increase in emphysema with increasing GOLD spirometry grade as measured by both density analysis (emphysema) and PRM (PRM^{emph}) and an increase in small airways disease (PRM^{fSAD}).

FEV_1 Change over Time

The median follow-up time for the entire cohort was 64 months (range, 49–79) with a

Table 1. Baseline Demographics

Total number of subjects (*N = 1,508*)	GOLD Spirometry Grade				
	0 (*n = 751*)	1 (*n = 150*)	2 (*n = 356*)	3 (*n = 192*)	4 (*n = 59*)
Age, yr	58.2 (8.6)	63.8 (8.1)	63.3 (8.4)	64.1 (7.9)	62.8 (7.6)
Sex, n (% female)	395 (52.6)	66 (44.0)	161 (45.2)	87 (45.3)	29 (49.2)
Race, n (% African American)	245 (32.6)	28 (18.7)	79 (22.2)	36 (18.8)	5 (8.5)
Height, cm	169.5 (9.2)	169.7 (10.1)	170.9 (9.3)	169.9 (10.3)	169.6 (9.0)
FEV_1, L	2.8 (0.7)	2.6 (0.7)	1.9 (0.5)	1.2 (0.3)	0.68 (0.2)
$FEV_{1\%}$ predicted	97.7 (11.4)	91.6 (8.6)	65.0 (8.3)	40.9 (5.9)	23.6 (4.1)
FVC, L	3.6 (0.9)	4.1 (1.0)	3.3 (0.9)	2.7 (0.8)	2.3 (0.6)
FVC % predicted	96.2 (11.3)	108.5 (11.2)	87.4 (13.4)	72.4 (12.8)	59.1 (11.6)
FEV_1/FVC	0.79 (0.1)	0.64 (0.04)	0.47 (0.08)	0.44 (0.09)	0.31 (0.05)
Smoking pack-years	37.2 (20.0)	40.0 (49.2)	37.9 (48.6)	55.4 (24.8)	57.8 (28.6)
Current smokers, n (%)	364 (48.5)	60 (40.0)	135 (37.9)	60 (31.3)	10 (16.9)
Bronchodilator reversibility, n (%)*	68 (9.1)	42 (28.0)	136 (38.2)	80 (41.7)	19 (32.2)
Exacerbations in the prior year	0.13 (0.49)	0.13 (0.37)	0.43 (0.95)	0.71 (1.15)	1.14 (1.50)
Follow-up time, mo	63.9 (4.5)	63.7 (4.2)	64.1 (4.2)	64.0 (4.1)	65.0 (5.1)
Emphysema, %LAA <-950 HU_{insp}	2.7 (3.0)	6.9 (6.4)	8.4 (8.4)	17.9 (12.6)	26.6 (13.6)
Gas trapping, %LAA <-856 HU_{exp}	11.8 (9.9)	23.4 (12.1)	29.9 (15.4)	48.7 (16.3)	60.9 (12.2)
PRM functional small airways disease, %	12.4 (9.7)	22.2 (10.7)	26.6 (11.6)	36.3 (10.0)	39.2 (9.9)
PRM emphysema, %	0.6 (1.4)	3.3 (4.4)	5.6 (7.4)	15.2 (12.9)	24.7 (14.7)

Definition of abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAA <-856 HU_{exp} = low-attenuation areas <-856 Hounsfield units at end expiration; LAA <-950 HU_{insp} = low-attenuation areas <-950 Hounsfield units at end inspiration; PRM = parametric response mapping. All values expressed as mean (SD) except categorical variables expressed as n (%).
*Bronchodilator reversibility defined as 12% and 200-ml increase in FEV_1 and/or FVC.

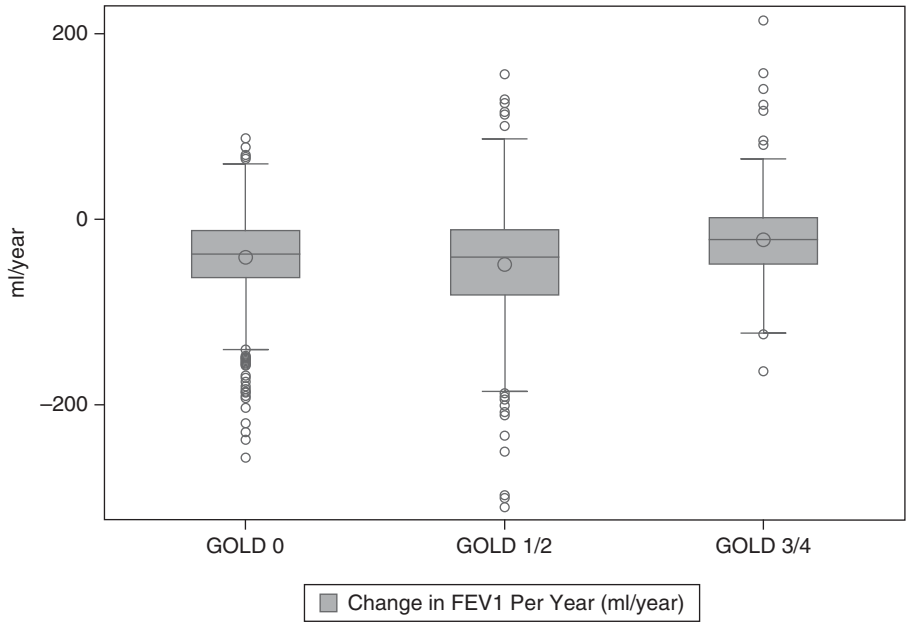

Figure 2. Change in FEV_1 (ml/yr) between visit 1 and visit 2 by disease stage. Figures show the proportion of subjects in each disease stage group with varying levels of change in FEV_1 (ml/yr) over a 5-year period for GOLD (Global Initiative for Obstructive Lung Disease) 0, mean −41.8 (47.7) ml/yr; GOLD grades 1 and 2 combined, mean −48.0 (SD, 60.0) ml/yr; and GOLD grades 3 and 4 combined, mean −25.3 (SD, 43.3) ml/yr.

mean (SD) rate of decline in FEV_1 of 41.1 (52.0) ml/yr (Figure 2). For GOLD 0 participants, mean rate of FEV_1 decline was 41.8 (47.7) ml/yr. Those with GOLD grade 1 had the most rapid rate of decline of 53.8 (57.1) ml/yr, with progressively slower rates of decline with increasing GOLD grades: 45.6 (61.1), 31.6 (43.6), and 5.1 (35.8) for GOLD grades 2–4, respectively (trend test for grades 1–4; $P < 0.001$). Figure E3 demonstrates that FEV_1 decline expressed as change in percent predicted follows similar trend to FEV_1 change in milliliters.

Clinical Predictors of FEV_1 Change

The rate of FEV_1 change was strongly associated with several baseline demographic variables. Univariate and multivariable analyses for FEV_1 decline are presented in Tables E1 and E2. In multivariable analysis, FEV_1 decline (ml/yr) was greater in current versus former smokers (6.91 ml/yr greater decline; 95% confidence interval [CI], 0.82–13.01; $P = 0.01$). Those with baseline bronchodilator reversibility had greater FEV_1 decline compared with those without bronchodilator reversibility (18.80 ml/yr greater decline; 95% CI, 12.60–25.01; $P < 0.001$). Greater rates of FEV_1 decline were also seen with higher baseline FEV_1 (14.45 ml/yr decline per liter; 95% CI, 6.75–22.14; $P < 0.001$), higher baseline FVC (14.74 ml/yr decline per liter; 95% CI, 8.15–21.32; $P < 0.001$) and more smoking pack-years (1.43 ml/yr decline per 10 pack-years; 95% CI, 0.82–2.57; $P = 0.01$). Exacerbations in the prior year demonstrated no significant association with FEV_1 decline in either the univariate ($P = 0.38$) or multivariable model ($P = 0.55$) and, therefore, was not retained in the final model. African American race was associated with more rapid decline compared with non-Hispanic white participants (11.30 ml/yr greater decline; 95% CI, 4.34–18.25; $P = 0.002$) in multivariable analysis. Female sex was associated with more rapid FEV_1 decline than males (8.39 ml/yr greater decline; 95% CI, 0.94–15.84; $P = 0.03$); our analysis was not designed to assess sex difference.

Quantitative Imaging and FEV_1 Change

Results for the overall model are in Table E2. For all subjects, both PRM^{fSAD} and PRM^{emph} had a statistically significant association with lung function decline. To understand the impact of CT assessment of small airways disease and emphysema on FEV_1 decline based on presence or absence of baseline airflow obstruction, we also performed separate linear regression models for GOLD 0 and GOLD 1–4 subjects. Parameter estimates for the CT metrics for these stratified models are presented in Table 2.

Table 2. Association between PRM Emphysema and fSAD on Change in FEV_1 ml/Year by Baseline GOLD Grade (Estimate, 95% CI, *P* Value)

	PRM^{fSAD}	PRM^{emph}
GOLD 0 (n = 751)		
Parameter estimate per 5% (ml/yr)	−2.2 (95% CI, −4.2 to −0.1; $P = 0.04$)	5.5 (95% CI, −8.0 to 19.1; $P = 0.42$)
Mean value CT metric (%)	12.4 (9.7)	0.6 (1.4)
GOLD 1–4 (n = 757)		
Parameter estimate per 5% (ml/yr)	−4.5 (95% CI, −6.3 to −2.6; $P < 0.001$)	−3.5 (95% CI, −5.6 to −1.4; $P = 0.001$)
Mean value CT metric (%)	29.2 (12.3)	9.1 (11.4)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; fSAD = functional small airways disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRM = parametric response mapping; PRM^{emph} = emphysema on parametric response mapping; PRM^{fSAD} = functional small airways disease on parametric response mapping.
Two separate models are shown in rows for the groups GOLD 0 and GOLD 1–4 subjects. Parameter estimates and mean values for respective CT metrics are shown. All models adjusted for age, race, sex, height, current smoking, smoking history in pack-years, baseline FEV_1, baseline FVC, bronchodilator reversibility, and scanner type.

Among GOLD 0 participants, PRM^{fSAD} but not PRM^{emph} was significantly associated with FEV_1 decline. For every additional 5% of lung affected by PRM^{fSAD}, a significant decline in FEV_1 was seen (2.2 ml/yr per 5% PRM^{fSAD}; $P = 0.04$). Among GOLD 1–4 participants, for every additional 5% of lung affected by PRM^{fSAD} or PRM^{emph} a significant decline in FEV_1 was seen (4.5 ml/yr; 95% CI, 6.3–2.6; $P < 0.001$ and 3.5 ml/yr; 95% CI, 5.6–1.4; $P = 0.001$, respectively).

We also sought to understand the contribution of CT metrics to FEV_1 decline relative to each other in milder versus more severe disease (*see* Figure E4). We therefore used the parameter estimates from the linear regression model and mean CT metric values corresponding to GOLD 1–2 and GOLD 3–4 groups to determine the relative contribution of PRM^{fSAD} and PRM^{emph} to FEV_1 decline. PRM^{fSAD} was associated with significantly greater FEV_1 decline than PRM^{emph} for both groups ($P = 0.001$ for GOLD1–2; $P = 0.007$ for GOLD 3–4), although this was even more pronounced for the GOLD 1–2 group (87% vs. 13% and 68% vs. 32% for PRM^{fSAD} and PRM^{emph} in GOLD 1–2 and 3–4, respectively).

Finally, to better understand the significance of PRM^{fSAD} in the GOLD 0 group, we also examined the mean rate of decline for varying levels of PRM^{fSAD}. As previously stated, the mean change in FEV_1 for GOLD 0 group was 41.8 (47.7) ml/yr. For individuals at or above the median PRM^{fSAD} level for the GOLD 0 group (PRM^{fSAD} 11%), the mean decline in FEV_1 was 45.2 (47.8) ml/yr versus 38.6 (47.2) ml/yr for those below the median ($P = 0.05$). For individuals at or above the 75th percentile of PRM^{fSAD} for GOLD 0 group (PRM^{fSAD} 16%) the mean decline in FEV_1 was 49.2 (50.2) ml/yr compared with those below the 75th percentile at 39.0 (46.4) ($P = 0.009$). Table E3 shows mean FEV_1 decline across quartiles of PRM^{fsad} for GOLD 0.

Discussion

We demonstrated that, in a cohort of current and former smokers, functional small airways disease as measured by chest CT is associated with subsequent FEV_1 decline. Although we showed that emphysema is also associated with FEV_1 decline, its impact relative to small airway abnormality is weaker, particularly in mild-to-moderate disease stage. Finally, we demonstrated that this association between functional small airways disease and FEV_1 decline is evident in GOLD 0 subjects even before the development of spirometrically detected airflow obstruction.

Our findings support prior pathologic investigations of COPD. The small airways less than 2 mm in diameter are the major site of increased airflow resistance in COPD as established first in the 1960s through retrograde catheter studies in post-mortem lungs (3) and then later in living lungs (4). Peripheral airway inflammation has been noted in young smokers even before COPD is established (18). Further increases in this inflammatory response along with development of airway wall structural abnormalities have also been described in established COPD resulting in airway lumen narrowing (6). Recent histologic and micro CT data also reveal that narrowing and disappearance of terminal bronchioles precedes the development of emphysema (6).

Previously it has been demonstrated in individuals with moderate to severe COPD that emphysema on CT, defined as the percentage of voxels with density less than −950 HU at full inspiration, is associated with a more rapid decline of FEV_1 (9, 19). However, a good way to assess the small airways in patients radiographically has been lacking. Gas trapping, measured as the percent of voxels less than −856 HU using expiratory images alone, is limited by the inability to distinguish small airways disease from emphysema (7). Unlike standard densitometric analyses using inspiratory or expiratory images in isolation, PRM digitally coregisters inspiratory and expiratory CT images, which should help distinguish small airways disease from emphysema (8).

Here we demonstrated, in a large cohort of current and former smokers with a broad spectrum of disease severity, that functional small airways disease on CT as measured by PRM is significantly associated with decline in FEV_1 particularly in mild-to-moderate stage disease, whereas the contributions of small airways disease and emphysema are relatively more equal in later stages (GOLD 3–4). This association between functional small airways disease and FEV_1 decline was evident even before the development of spirometrically detected airflow obstruction. We do note, however, that the effect size for PRM^{fSAD} was attenuated in GOLD 0 individuals as compared with those with established airflow obstruction. We postulate that airway disease if present in smokers without airflow obstruction may still be of a reversible nature and may represent bronchospasm or inflammation as opposed to fibrosis or airway loss.

In prior work comparing paired CT scans in smokers with GOLD 0–4 disease performed at 30 days and 1 year apart, we demonstrated particularly in individuals with mild-to-moderate stage disease that PRM^{fSAD} may increase or decrease over these shorter time intervals suggesting a reversible component (20). Here we demonstrated that in those with established airflow obstruction, PRM^{fSAD} is strongly associated with FEV_1 decline. Although PRM^{emph} was also associated with FEV_1 decline, its relative impact was weaker, particularly in mild-to-moderate disease. This is not to say, however, that emphysema as defined by PRM in mild-to-moderate stage disease is not important when present, but it is generally lesser in magnitude than small airways disease. We also demonstrated that high levels of CT-defined small airway abnormality were present in individuals without airflow obstruction who subsequently experience more rapid declines in FEV_1. In fact, the rate of decline experienced by GOLD 0 participants with PRM^{fSAD} greater than median value (45.2 ml/yr) was comparable with the rate of decline experienced by GOLD 2 individuals (45.6 ml/yr). These findings have potential implications for identifying individuals without airflow obstruction but at high risk for more rapid lung function decline.

Our study has several potential limitations. We had only two measurements of lung function separated by a median of approximately 5 years. However, within-person variability in our results was offset by the large number of individuals used to estimate average change. We also did not have data on lifelong FEV_1 trajectories (21); however, our goal was primarily to examine the relative impact of structural lung disease on subsequent FEV_1 decline. Our analysis was based on subjects who had completed their second study visit by November 3, 2014. It is possible that

patients who were first to follow-up differ from those who were either late for their second visit or lost to follow-up. Many of the patients with airflow obstruction were receiving therapy for their disease. Although no existing pharmacotherapy has been conclusively shown to affect the rate of FEV_1 decline, this still may have influenced our results. However, we chose not to include pharmacotherapy data in these analyses to reduce biases inherent to patient-reported pharmacoepidemiologic data (22).

We also describe an imaging metric that measures "functional" small airways disease through the change in lung density seen between inspiration and expiration. It is not a direct measure of airway thickness or destruction. The lack of a normal increase in lung density between inspiration and expiration implies that air is trapped. We postulate that such air trapping is caused by small airways disease, but the exact contribution of larger visible and smaller nonvisible airways is actively being investigated with radiologic-pathologic correlation. In addition, this algorithm assigns every voxel to a specific disease category, which likely represents the majority of abnormality, but in reality there may be a mix of histologic abnormalities in the tissue covered by one voxel. The goal for the expiratory images was to obtain images at functional residual capacity. It is possible that this underestimates the amount of air trapping that might be seen at residual volume.

The current study also has a number of strengths. PRM is an advance over the traditional "gas trapping" metric defined by voxels less than −856 HU on expiration, which likely combines true emphysema and small airway abnormality (7). Here we allow the relative contribution from each to be resolved. Analyses were performed within a well-characterized cohort that included subjects with all stages of disease severity represented proportionally and with stringent spirometry and CT quality control. PRM metrics provide a novel noninvasive CT biomarker for disease progression, particularly in mild to moderate COPD. Even though there are no established therapies to treat lung function decline, early identification of these subjects allows prognostication and perhaps targeting novel therapies in these individuals using the detailed spatial information provided on disease distribution and relative contribution of small airways disease and emphysema.

Conclusions

Both CT-assessed functional small airways disease and emphysema are associated with FEV_1 decline, but the association with functional small airways disease has greatest importance in mild-to-moderate stage COPD where the rate of FEV_1 decline is the greatest. These findings are consistent with prior pathologic studies and allow a noninvasive means to target at-risk patients at milder stages of the disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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