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Voxel-Wise Longitudinal Parametric Response Mapping Analysis of Chest Computed Tomography in Smokers

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Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by small airway abnormality and emphysema. We hypothesized that a voxel-wise CT analytic approach would identify patterns of disease progression in smokers.

Methods: We analyzed 725 smokers with two chest CTs five years apart. Voxel-wise Parametric Response Mapping (PRM) analysis was applied to baseline inspiration, follow-up inspiration and follow-up expiration images. PRM classifies lung as normal (PRM^{NORM}), functional small airway disease (PRM^{fSAD}) and emphysema (PRM^{EMPH}). These images were spatially registered to the baseline expiration image so that each voxel had correspondences across all time points and respiratory phases.

Results: Subjects with low baseline PRM^{fSAD} and PRM^{EMPH} predominantly had an increase in PRM^{fSAD} on follow-up; those with higher baseline PRM^{fSAD} and PRM^{EMPH} mostly had increases in PRM^{EMPH}. For GOLD 0 participants (n=419), mean increases in 5-year PRM^{fSAD} and PRM^{EMPH} were 0.3% for both; for GOLD 1-4 participants (n=306), they were 0.6% and 1.6%, respectively. Eighty GOLD 0 subjects (19.1%) had overall radiologic progression (30.0% to PRM^{fSAD}, 52.5% to PRM^{EMPH}, 17.5% to both); 153 GOLD 1-4 subjects (50.0%) experienced progression (17.6% to PRM^{fSAD}, 48.4% to PRM^{EMPH}, 34.0% to both). In a multivariable model,

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both baseline PRM^{fSAD} and PRM^{EMPH} were associated with development of PRM^{EMPH} on follow-up, although this relationship was diminished at higher levels of baseline PRM^{EMPH} .

Conclusion: A voxel-wise longitudinal PRM analytic approach can identify patterns of disease progression in smokers with and without COPD.

Keywords

chronic obstructive pulmonary disease; computed tomography; Parametric Response Mapping; small airway disease; emphysema

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by small airway abnormality and emphysema (1). While emphysema is a prominent feature of severe disease, little is known about the stages and timeline of its progression on a radiological level. Parametric Response Mapping (PRM) analysis which incorporates information from both inspiratory and expiratory computed tomography (CT) images is one way to quantitatively assess this data. PRM captures the change in lung density between matched inspiratory and expiratory images (2), thereby enabling the distinction between normal lung parenchyma (PRM^{NORM}), emphysema (PRM^{EMPH}) and non-emphysematous air trapping referred to as functional small airway disease (PRM^{fSAD}).

However, the analysis of longitudinal quantitative CT data is challenging and optimal methods have not been firmly established, particularly for PRM data. Here we conduct an analysis of a large multicenter study of current and former smokers to characterize changes in PRM^{fSAD} and PRM^{EMPH} over 5 years of follow-up using voxel-wise co-registration of the baseline and follow-up images to characterize patterns of progression in smokers with and without COPD. We limited this analysis to participants who had both their initial and follow-up chest CTs with identical scanning parameters and comparable lung volumes between the two scans to minimize variability in the data. We hypothesized that baseline PRM^{fSAD} is a radiographic precursor to emphysema.

METHODS

Study participants and design

COPDGene is a multicenter longitudinal cohort study that enrolled more than 10,000 current and former smokers with at least a 10 pack-year smoking history, with and without airflow obstruction (3). We analyzed 725 subjects in GOLD (Global initiative for chronic Obstructive Lung Disease) stages 0-4 who had chest CTs performed on two visits approximately 5 years apart with the same scanner make and model and 15% difference in inspiratory lung volumes between the two scans. Subjects with mismatches in other specific scanning parameters between the two visits were also excluded (see Supplementary Figure 1). Data on demographics, smoking history, respiratory symptoms, comorbidities and exacerbation history were collected at the baseline visit. The modified Medical Research Council score was used to assess dyspnea severity (4) and the St. George's Respiratory Questionnaire was used to evaluate quality of life and respiratory impairment (5).

Exacerbations were defined as acute worsening of respiratory symptoms necessitating treatment with antibiotics and/or systemic corticosteroids. Spirometry was performed at both visits before and after administration of 180 µg of albuterol. Airflow obstruction was defined as post-bronchodilator FEV₁/FVC (forced expiratory volume in the first second over forced vital capacity) less than 0.7 and staged according to the GOLD guidelines (6). GOLD 0 was defined by post-bronchodilator FEV₁/FVC greater than 0.7 with FEV₁ greater than 80% predicted regardless of symptom burden. Bronchodilator reversibility was defined as an increase of at least 200 ml and 12% in FEV₁ and/or FVC (7). The study protocol was approved by the institutional review boards of all participating centers and all subjects gave written informed consent.

Computed tomography protocol and Parametric Response Mapping analysis

For both study visits, paired inspiratory and expiratory chest CTs were obtained at maximal inspiration (total lung capacity) and end-tidal expiration (functional residual capacity) (3). An image processing workflow was designed for voxel-wise longitudinal analysis of PRM. The baseline inspiration, follow-up inspiration, and follow-up expiration images were spatially registered to the baseline expiration so that each voxel had correspondences across all time points and respiratory phases (see Supplementary Figure 2). Following image registration, the Hounsfield Unit (HU) values for lung voxels in the baseline scan were adjusted to account for differences in ventilation level across time points using a sponge model method based on lung volumes (8). The following equation was used:

$$CT_{adjusted_baseline}(\vec{x}) = (CT_{baseline}(\vec{x}) + 1000HU) \frac{V_{baseline}}{V_{follow-up}} - 1000HU$$

where V represents the total lung volume obtained from a segmentation of the left and right lungs on the CT image. Parametric Response Maps were then generated for the baseline and follow-up time points by Imbio LLC (Minneapolis, MN, USA) (2). Briefly, all voxels < -950 HU on the inspiration scan were classified as PRM^{EMPH}, voxels < -950 HU on the inspiration scan and < -856 HU on the expiration scan were classified as PRM^{fSAD}, and voxels < -950 HU on the inspiration scan and < -856 HU on the expiration scan were classified as PRM^{NORM}.

A metric was then devised to measure the net changes in PRM categories over time. Given two arbitrary PRM categories A and B (e.g. normal and fSAD), PRM^{AB} change was defined as the number of individual voxels changing from category A to category B minus the number of individual voxels changing from category B to category A , normalized by the total number of voxels in the lung. This method allows for direct tracking of each voxel between the baseline and follow-up scans. Three types of net change were of interest to us: PRM^{NORMfSAD}, PRM^{NORMEMPH} and PRM^{fSADEMPH}. Thresholds for categorizing meaningful net changes were calculated using 30-day repeat scans from 57 GOLD 0-4 subjects enrolled in the SPIROMICS repeatability sub-study (9, 10). These subjects met the same scanning parameter matching criteria that we applied to the COPDGene subjects in our analysis, acknowledging however that SPIROMICS and COPDGene have differences in their quantitative CT protocols (3, 11). PRM^{NORMfSAD}, PRM^{NORMEMPH} and

PRM^{fSAD} changes were computed for each of the 57 subjects in the repeatability sub-study. Limits of agreement were used to define meaningful PRM changes (i.e. not due to noise or measurement error) and were computed as $1.96 \times$ standard deviation of each change category over all subjects. The following limits of agreement were found for each net change: PRM^{NORMfSAD}: 4.09%, PRM^{NORM EMPH}: 0.85% and PRM^{fSAD EMPH}: 1.35%. Using this model, subjects with PRM change greater than the limits of agreement were defined as progressors and classified into one of three types of longitudinal patterns: overall progression to fSAD, overall progression to emphysema or progression to both. Lungs were also segmented cranio-caudally into upper, middle and lower zones for regional analysis.

Statistical analyses

We first described baseline clinical characteristics of GOLD 0 and GOLD 1-4 participants. Continuous variables were reported as means and standard deviations and categorical ones as percentages. To compare these baseline characteristics between GOLD 0 and GOLD 1-4 subjects, a t-test was conducted for continuous variables and a Pearson's chi-square test was performed for categorical ones. The association of baseline chest CT PRM metrics with change in total lung PRM^{EMPH} between the two visits was tested using a multivariable linear regression model adjusted for age, gender, race, smoking history, current smoking status, FEV₁, FVC, bronchodilator response and scanner type. Based on exploration of potential spline terms, a spline interpolation was included in the model at a PRM^{EMPH} cutoff of 10% as any additional amount of baseline PRM^{EMPH} beyond this threshold was found to be negatively associated with increase in follow-up PRM^{EMPH}. Given the small amount of 5-year total emphysema change noted in GOLD 0 participants, we conducted additional analyses with the same multivariable model using PRM metrics of segmented lung zones (upper, middle and lower). All analyses were performed in R software version 3.3. A p-value less than 0.05 was considered statistically significant.

RESULTS

Among the 725 participants included in our analysis, 419 (57.8%) were in GOLD stage 0 and 306 (42.2%) were in GOLD stages 1-4. A description of subject characteristics at the baseline visit is presented in Table 1. Compared to GOLD 0 participants, those with GOLD 1-4 spirometry were older, less likely to be African-American and had a greater smoking history, higher dyspnea scores, poorer quality of life, worse exertional capacity and more respiratory exacerbations in the preceding year. Among the 306 GOLD 1-4 subjects, mean PRM^{fSAD} increased from 24.6% to 25.2% and mean PRM^{EMPH} increased from 9.6% to 11.2% after 5 years of follow-up (**Table 2**); 153 individuals (50.0%) had overall progression to fSAD and/or emphysema based on the pre-specified thresholds. Compared to non-progressors, progressors had a higher baseline PRM^{fSAD} (28.6% vs. 20.7%) and PRM^{EMPH} (12.8 vs. 6.3%) as well as worse baseline lung function (FEV₁ % predicted 57.4% vs. 64.3%). Among the 419 GOLD 0 subjects, mean PRM^{fSAD} increased from 9.5% to 9.8% and mean PRM^{EMPH} increased from 2.0% to 2.3% after 5 years of follow-up (Supplementary Table 1); 80 individuals (19.0%) had overall progression to fSAD and/or emphysema. Similar to GOLD 1-4, compared to non-progressors, GOLD 0 progressors had

a higher baseline PRM^{fSAD} (12.9% vs. 8.7%) and PRM^{EMPH} (4.1% vs. 1.6%), but similar FEV₁ % predicted.

Figure 1 shows the trajectories of PRM metric changes between the baseline and follow-up visits by pattern of CT progression (overall to fSAD, overall to emphysema or to both) for GOLD 0 and GOLD 1-4 progressors. For these subjects, progression to emphysema occurred almost equally in both groups (52.5% of GOLD 0 and 48.4% of GOLD 1-4 progressors). Progression to PRM^{fSAD} was more frequent in GOLD 0 than GOLD 1-4 (30.0% versus 17.6%, respectively). Progression to both PRM^{fSAD} and PRM^{EMPH} was more frequent in GOLD 1-4 than GOLD 0 (34.0% versus 17.5%, respectively). GOLD 1-4 participants who had overall progression to PRM^{EMPH} experienced a concurrent decline in PRM^{fSAD} over the 5 years of follow-up (trajectory B in Figure 1).

In the multivariable model for all GOLD 1-4 participants, both baseline PRM^{fSAD} and PRM^{EMPH} (below the 10% spline cutoff) were independent predictors of an increase in total lung PRM^{EMPH} over 5 years of follow-up (**Table 3**); every additional 1% in baseline PRM^{fSAD} and PRM^{EMPH} was associated with a 0.05% and 0.19% increase in follow-up total lung PRM^{EMPH}, respectively. Currently smoking status at baseline was also significantly associated with a subsequent increase in total PRM^{EMPH}. Our model also suggests that the impact of baseline PRM^{EMPH} on the subsequent development of emphysema is attenuated at higher levels based on the effect of the spline term at the 10% cutoff. For example, suppose we examine a currently smoking, African-American woman with the same mean age, spirometry and pack-years smoked as our GOLD 1-4 cohort (listed in Table 1) and no bronchodilator response. A fitted curve was used to estimate the amount of baseline fSAD for a given amount of baseline emphysema (Supplementary Figure 3). For this hypothetical patient, baseline PRM^{EMPH} of 10% with corresponding PRM^{fSAD} of 29.0% would be associated with a predicted five-year increase in PRM^{EMPH} of 4.0%. For that same patient, if baseline PRM^{EMPH} is 20% with corresponding PRM^{fSAD} of 32.9%, the predicted five-year increase in PRM^{EMPH} would be 1.9%.

To illustrate our findings radiographically, we show the 5-year interval PRM changes on chest CT of a 58-year old man with COPD in GOLD stage 2 (Figure 2). This participant experienced progression of his COPD as reflected by decrease in his FEV₁ from 57% to 30% predicted and increase in his PRM^{EMPH} from 24% to 35% of total lung volume. Panel B of Figure 2 shows the conversion of individual voxels from PRM^{fSAD} to PRM^{EMPH} after 5 years, which supports the association we found in our model between baseline fSAD and increase in follow-up emphysema.

The overall mean 5-year change in PRM^{EMPH} for the GOLD 0 group was quite small (0.29%). Therefore, for this group, we chose to model change in upper lung PRM^{EMPH} where the 5-year change was greatest (0.39%, 0.27% and 0.21% for upper, middle and lower zones respectively; p-value = 0.02 for difference between upper and lower zones). In this model, both upper lung PRM^{fSAD} and PRM^{EMPH} were predictive of an increase in upper lung PRM^{EMPH} after 5 years of follow-up (Supplementary Table 2).

DISCUSSION

In a large prospective cohort of current and former smokers with and without COPD, we demonstrate the ability of a voxel-wise, longitudinal PRM approach to characterize patterns of radiologic progression. We show that progression is typified by increases in PRM^{fSAD}, followed by increases in PRM^{EMPH} with overall less progression among GOLD 0 individuals as compared to GOLD 1-4. Over the five-year period, progression for both GOLD 0 and GOLD 1-4 subjects was most frequently characterized by transition of normal or fSAD lung to emphysema. Our multivariable models support this finding by demonstrating that PRM^{fSAD} and PRM^{EMPH} are independent predictors of future emphysema development.

Multiple studies have suggested that small airway disease is a precursor to emphysema. In explanted lungs from COPD patients undergoing transplantation, micro CT and histologic examination of terminal bronchioles in areas with variable emphysema severity showed that the narrowing and loss of these airways occurred before emphysematous destruction (12). Our findings support the results of smaller, prior cross-sectional and short-term longitudinal studies (2, 13) by demonstrating that baseline PRM^{fSAD} on chest CT is independently associated with an increase in emphysema 5 years later. Our study also suggests that the pattern of radiographic disease progression is marked by an increase in PRM^{fSAD} that is attenuated as emphysema increases.

Emphysema is characterized by permanent dilatation of air spaces and destruction of their walls distal to terminal bronchioles (14), resulting in loss of elastic recoil, impaired gas exchange and lung hyperinflation. However, the negative impact of emphysema may extend beyond affected areas to involve adjacent normal lung parenchyma by subjecting it to significant mechanical stretch during respiration. Some proposed mechanisms of this effect include abnormal remodeling of the extracellular matrix and increased binding of elastase to elastin (15-17), thereby generating a positive feedback loop. By virtue of its presence, emphysema may predispose the surrounding lung to more emphysema. Bhatt and colleagues showed that the Jacobian determinant (a biomechanical metric reflecting the degree of lung deformation) of normal voxels within 2 mm of emphysematous voxels was associated with lung function decline (18). In another analysis of the COPDGene cohort, the Jacobian determinant was also shown to be an independent predictor of increased respiratory impairment, worse exertional capacity and a higher BODE index in individuals with COPD (19). The results of our analysis are concordant with these findings and support the notion of “emphysema begetting emphysema” (20).

Our study extends the findings of a prior report demonstrating an association between baseline PRM^{fSAD} and PRM^{EMPH} with subsequent FEV₁ decline in GOLD 1-4 subjects (21). From a histologic standpoint, one might hypothesize that earlier in the course of disease, PRM^{fSAD} on chest CT represents a mixture of pathologic abnormalities ranging from inflamed airways with potentially reversible damage to fibrotic or even lost airways (22). The amount of PRM^{fSAD} in a given individual may then represent the pool of lung at risk for transition to emphysema. However, the presence of even small amounts of emphysema may indicate the potential for irreversible transformation. Therefore, the

susceptibility of each individual with COPD to experience disease progression depends, at least partially, on their biologic milieu of existing airway inflammation and alveolar loss. From a clinical perspective, early identification of subjects at risk for emphysema progression is important as emphysema has been independently associated with a number of adverse outcomes including lung function decline (23), respiratory exacerbations (24), lung cancer (25, 26) and all-cause mortality (27).

We also demonstrate that progression of emphysema among GOLD 0 individuals is greatest in the upper lobes. Furthermore, the presence of baseline PRM^{fSAD} and PRM^{EMPH} in the upper lung zones is independently predictive of an increase in upper lung emphysema over time. Similarly, in another study of the COPDGene cohort, Boueiz and colleagues performed a cluster analysis on CT subtypes and found that the cluster most characterized by upper-lobe predominant emphysema at baseline experienced faster overall progression of emphysema (28). This differential effect by baseline emphysema distribution may be related to variability in regional perfusion (29), mechanical stress (30) and clearance of smoking metabolites (31) between the upper and lower parts of the lung. It is well known that emphysema tends to establish itself in the upper lobes first, although the etiology of this is not well understood.

We acknowledge limitations to our study. We selected participants who had both of their chest CTs performed with the same scanning parameters and had 15% difference in inspiratory lung volumes between the two visits in order to maximize the sensitivity of the analysis. Further investigations are needed in order to understand how to adapt this method when additional variability is introduced such as changes in scanner type or more extreme differences in lung volumes. We also do not control for pharmacologic therapy received by participants during the study. It is difficult to estimate the actual effect of pharmacotherapy on our findings as subjects could have been on multiple varying combinations of therapies throughout the 5-year duration of follow-up. In summary, we demonstrate the ability of a voxel-wise, longitudinal PRM approach to characterize patterns of radiologic progression in smokers with and without COPD and show that PRM^{fSAD} appears to be a radiologic precursor to emphysema.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATIONS (in alphabetical order)

COPD	chronic obstructive pulmonary disease
CT	computed tomography
EMPH	emphysema
FEV₁	forced expiratory volume in the first second
fSAD	functional small airway disease
FVC	forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
HU	Hounsfield Units
NORM	Normal

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Figure 1: Five-year change of chest CT Parametric Response Mapping metrics in GOLD 0 and GOLD 1-4 progressors

The center of each circle represents the mean coordinates (% PRM^{EMPH} and % PRM^{fSAD}) for each type of progression (to fSAD [A], emphysema [B] or both [C]) at the baseline and follow-up visits (identified by the direction of the arrows). The area of each circle is proportional to the number of subjects with a given type of progression (A, B or C) within their GOLD category (0 or 1-4).

Figure 2: Illustration of Parametric Response Mapping (PRM) changes on chest CT of a 58-year old man with COPD

(A) Longitudinal PRM changes on representative coronal CT slices showing normal lung parenchyma (green), functional small airway disease [fSAD] (yellow) and emphysema (red). (B) CT slices highlighting individual voxels that were classified as fSAD at baseline and became emphysema 5 years later in that same subject.

Table 1

Baseline characteristics of study participants

	GOLD 0 (n=419)	GOLD 1-4 (n=306)	p-value
Demographics			
Age	57.4 (8.5)	63.1 (8.3)	< 0.001
Female (%)	219 (52.3%)	153 (50.0%)	0.55
African-American (%)	153 (36.5%)	86 (28.1%)	0.02
Smoking exposure			
Smoking history (pack-years)	36.2 (19.4)	47.2 (21.8)	<0.001
Current smoking (%)	210 (50.1%)	133 (43.5%)	0.07
Post-bronchodilator spirometry			
FEV ₁ (L)	2.84 (0.68)	1.72 (0.73)	< 0.001
FEV ₁ % predicted	97.7 (11.1)	60.8 (21.8)	< 0.001
FVC (L)	3.62 (0.88)	3.05 (0.95)	< 0.001
FVC % predicted	96.5 (11.6)	82.5 (19.2)	< 0.001
FEV ₁ / FVC	0.79 (0.05)	0.55 (0.11)	< 0.001
Markers of respiratory health			
mMRC score	0.7 (1.2)	1.6 (1.4)	< 0.001
Total SGRQ score	14.8 (16.2)	31.3 (21.3)	< 0.001
6-minute walking distance (m)	467.0 (109.4)	400.8 (118.0)	< 0.001
Exacerbation frequency in past 12 months	0.2 (0.5)	0.5 (0.9)	< 0.001

Data are expressed as mean (standard deviation) except when stated and represent parameters from the baseline visit. FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; mMRC, modified medical research council; SGRQ, St. George's Respiratory Questionnaire. The mMRC score ranges from 0 to 4 with higher scores indicating worse dyspnea. The SGRQ score ranges from 0 to 100 with higher scores indicating a higher respiratory burden and worse quality of life.

Table 2

Spirometry and PRM chest CT metrics for GOLD 1-4 participants at the baseline and follow-up visits

	ALL (n=306)		Non-progressors (n=153)		Progressors (n=153)	
Spirometry	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
FEV ₁ (L)	1.72 (0.73)	1.56 (0.73)	1.82 (0.70)	1.71 (0.72)	1.62 (0.75)	1.42 (0.71)
FEV ₁ % predicted	60.8 (21.8)	59.4 (23.7)	64.3 (20.8)	65.0 (22.8)	57.4 (22.3)	53.9 (23.3)
FEV ₁ / FVC	0.55 (0.11)	0.55 (0.14)	0.59 (0.10)	0.59 (0.13)	0.52 (0.11)	0.50 (0.14)
Chest CT metrics	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
% PRM ^{fSAD}	24.6 (13.5)	25.2 (12.6)	20.7 (12.4)	20.1 (12.0)	28.4 (13.5)	30.3 (11.0)
% PRM ^{EMPH}	9.6 (10.6)	11.2 (11.7)	6.3 (8.6)	5.9 (7.9)	12.8 (11.4)	16.3 (12.4)

Data are expressed as mean (standard deviation). FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; % PRM^{fSAD} and % PRM^{EMPH}, total lung percent of functional small airway disease and emphysema on chest CT Parametric Response Mapping analysis.

Table 3

Model showing the associations between clinical and radiological variables at baseline and the 5-year change in total lung PRM^{EMPH} for all GOLD 1-4 participants

	Estimate	95% CI	p-value
Age, per 1-year	−0.007	−0.05; 0.04	0.78
Female	0.16	−0.52; 0.84	0.64
African-American	0.35	−0.45; 1.14	0.40
Smoking history, per 1 pack-year	0.02	−0.0007; 0.03	0.06
Current smoking	1.42	0.61; 2.22	0.0007
Post-bronchodilator FEV ₁ % predicted, per 1%	−0.02	−0.06; 0.03	0.42
Post-bronchodilator FVC % predicted, per 1%	0.03	−0.01; 0.07	0.19
Bronchodilator response	−0.23	−0.96; 0.50	0.53
Baseline PRM ^{fSAD} , per 1%	0.05	0.01; 0.09	0.009
Baseline PRM ^{EMPH} < 10%, per 1%	0.19	0.05; 0.33	0.007
Baseline PRM ^{EMPH} 10%, per 1%	−0.23	−0.40; −0.06	0.007

FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; PRM^{fSAD} and PRM^{EMPH}, total lung percent of functional small airway disease and emphysema on chest CT Parametric Response Mapping analysis. The model was also adjusted for scanner type. Spline term included at baseline PRM^{EMPH} 10%.