Computed Tomography Measure of Lung at Risk and Lung Function Decline in Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: The rate of decline of lung function is greater than age-related change in a substantial proportion of patients with chronic obstructive pulmonary disease, even after smoking cessation. Regions of the lung adjacent to emphysematous areas are subject to abnormal stretch during respiration, and this biomechanical stress likely influences emphysema initiation and progression.

Objectives: To assess whether quantifying this penumbra of lung at risk would predict FEV₁ decline.

Methods: We analyzed paired inspiratory-expiratory computed tomography images at baseline of 680 subjects participating in a large multicenter study (COPDGene) over approximately 5 years. By matching inspiratory and expiratory images voxel by voxel using image registration, we calculated the Jacobian determinant, a measure of local lung expansion and contraction with respiration. We measured the distance between each normal voxel to the nearest emphysematous voxel, and quantified the percentage of normal voxels within each millimeter distance from emphysematous voxels as mechanically affected lung (MAL). Multivariable regression

analyses were performed to assess the relationship between the Jacobian determinant, MAL, and FEV₁ decline.

Measurements and Main Results: The mean (SD) rate of decline in FEV₁ was 39.0 (58.6) ml/yr. There was a progressive decrease in the mean Jacobian determinant of both emphysematous and normal voxels with increasing disease stage ($P < 0.001$). On multivariable analyses, the mean Jacobian determinant of normal voxels within 2 mm of emphysematous voxels (MAL₂) was significantly associated with FEV₁ decline. In mild-moderate disease, for participants at or above the median MAL₂ (threshold, 36.9%), the mean decline in FEV₁ was 56.4 (68.0) ml/yr versus 43.2 (59.9) ml/yr for those below the median ($P = 0.044$).

Conclusions: Areas of normal-appearing lung are mechanically influenced by emphysematous areas and this lung at risk is associated with lung function decline.

Clinical trial registered with www.clinicaltrials.gov (NCT00608764).

Keywords: FEV₁; emphysema; image registration; biomechanical; lung at risk

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At a Glance Commentary

Scientific Knowledge on the

Subject: The rate of decline of lung function is greater than age-related change in a substantial proportion of patients with chronic obstructive pulmonary disease, even after smoking cessation. Regions of the lung adjacent to emphysematous areas are subject to abnormal stretch during respiration, and this biomechanical stress likely influences emphysema initiation and progression. Whether the regions of the lung surrounding emphysematous areas constitute lung at risk for disease progression is not known.

What This Study Adds to the

Field: In participants with emphysema, normal-appearing lung regions on computed tomography have abnormal regional expansion, and there is a spatial relationship between areas of emphysema and abnormal lung mechanics resulting in a penumbra of mechanically affected lung. Quantifying the amount of mechanically affected lung can independently predict lung function change over time.

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction, and the rate of decline of lung function is greater than age-related changes in a substantial proportion of patients, even after smoking cessation (1). COPD is the third leading cause of death in the United States and is associated with significant morbidity and health care costs (1). Progression of disease in COPD is variable, and although some patients have a relatively slow rate of lung function deterioration, others suffer an inexorable decline resulting in significant symptoms, respiratory failure, and mortality (2). Despite significant advances in phenotyping COPD and the development of markers to predict exacerbations and mortality (3), there is unfortunately a distinct lack of biomarkers that can help identify early disease and predict disease progression (4).

FEV₁ is affected by resistance to airflow in the small airways and the elastic recoil of the lung parenchyma (5). The

dominant pathogenetic mechanisms for COPD have involved proteinase-antiproteinase imbalance, oxidative stress, and inflammation (6, 7); however, biomarkers related to these pathways have not been shown to be useful in predicting disease progression. A less explored mechanism for emphysema initiation and progression is mechanical forces and stress fatigue (8). It is plausible that emphysema begets more emphysema, as regions of the lung adjacent to emphysematous regions are subject to abnormal forces of stretch during tidal respiration (9–13). At end expiration, the alveolar walls are under significant mechanical stress, and cyclical breathing imposes additional mechanical forces on already weakened elastin and collagen fibers, which over a long time can result in rupture of the alveolar wall in surrounding susceptible regions, effectively creating a penumbra (9, 12). Heterogeneity in regional lung expansion in COPD might be a reflection of these mechanical forces exerted by emphysematous areas.

Using image registration on paired inspiratory-expiratory images, voxels on inspiratory images can be matched with corresponding voxels on expiratory images, and a biomechanical metric called the Jacobian determinant, a measure of regional parenchymal volume change with respiration, can be calculated (14, 15). We hypothesized that regions of the lung in the penumbra around the areas of emphysematous lung would have abnormal mechanics, and that heterogeneity of regional lung expansion is associated with lung function decline. Using this metric for estimating lung mechanics, we assessed the areas surrounding emphysematous regions with normal appearance but with abnormal mechanics, which we called the mechanically affected lung (MAL). We also hypothesized that by enabling estimation of the regions subject to abnormal stretch, the percentage of MAL would predict lung function decline.

Methods

Study Population

We included 714 participants with Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1–4 disease enrolled in the COPDGene (Genetic Epidemiology of COPD) study and who completed a second

COPDGene visit approximately 5 years after the first visit by November 2014 (*see* Figure E1 in the online supplement). COPDGene is a large multicenter cohort of current and former smokers aged 45–80 years and with 10 or more pack-year smoking history; details of this study have been previously published (16). Participants with known lung disease other than COPD and asthma, or prior lobar excision, active malignancy, and chest radiation were excluded. All participants provided written informed consent and the study was approved by the institutional review boards of all 21 centers.

At enrollment and at follow-up, spirometry was performed before and after administration of 180 µg of albuterol (Easy-One spirometer; ndd, Andover, MA). Post-bronchodilator ratio of FEV₁ to FVC less than 0.70 at baseline was used to diagnose COPD, and severity of the disease was graded per the GOLD recommendations (1). Volumetric computed tomography (CT) scans were obtained at full inspiration (total lung capacity [TLC]) and end-tidal expiration (FRC). Subjects with CT images acquired at residual volume at one center were excluded (*see* online supplement). CT images were analyzed using Apollo software (VIDA Diagnostics, Inc., Coralville, IA) (16). Percentage emphysema was quantified by the low attenuation units less than −950 Hounsfield units (HU) at TLC, and gas trapping using the percentage of low attenuation units less than −856 HU at FRC using density mask analyses. Airway disease was quantified by the wall area percentage of segmental airways (WA%) (16).

CT Image Registration

Using image registration, we quantified regional lung expansion over 1 mm³ volumes. Image registration is a technique that finds the spatial relationship between two images (*see* online supplement) (14, 17). Briefly, after extraction of the airways, the FRC image is held fixed and the TLC image is transformed into the same coordinate system as the fixed image, thereby matching the images voxel for voxel. A lung mass-preserving registration method is used to capture local volume changes between the two phases. A deformation matrix is created to measure the deformation of lung tissue between inspiration and expiration

(14, 17). We calculated a derived variable termed the Jacobian determinant (see Figure E2), a measure of the regional volume change (across 1 mm³) caused by deformation of the lung from TLC to FRC; values range from 0 to infinity. Jacobian determinant greater than one indicates local expansion and less than one implies local contraction. We created deformation maps for the entire lung using the Jacobian determinant that included regions of emphysema and normal lung without emphysema. To test our hypothesis that areas of emphysematous lung influence the mechanics of normal regions of the

lungs, we calculated the Jacobian determinant separately for emphysematous and normal regions of the lung, and the coefficient of variation of the Jacobian determinant (CV Jacobian) to estimate the heterogeneity of regional expansion of the lung.

Spatial Relationship: Emphysema and Normal Regions

To improve anatomic localization, we created a distance map by plotting the Euclidean distance between each normal voxel to the nearest voxel with emphysema (Figure 1). The percentage of normal voxels within each millimeter distance from

emphysematous voxel was quantified (MAL).

Statistical Analyses

Univariate comparisons were made using two-tailed independent Student's *t* tests and analyses of variance with Tukey *post hoc* comparisons for continuous variables, and chi-square test for categorical variables. The primary outcome of change in FEV₁ was calculated by subtracting FEV₁ at enrollment from FEV₁ at follow-up, and annualized. Univariate and multivariable associations were tested between the CV of Jacobian determinant (separately for whole lung and normal areas) and change in

Figure 1. Graphic representation of the spatial mapping methodology showing spatial mapping for a representative subject. (A) Deformed inspiratory image with (B) emphysema regions (low-attenuation areas less than -950 Hounsfield units [HU]) highlighted in red on inspiratory computed tomography scan. (C) Example of emphysematous region in the lung. (D) Three-dimensional Euclidean distance-based clustering: distance was calculated for each normal voxel to the nearest emphysema voxel in three dimensions, and the surrounding normal tissue was clustered into different groups based on their spatial distance to the nearest emphysema voxels. Clustering of the surrounding tissue was performed in 1-mm increments up to 5 mm based on distance to nearest emphysematous voxels. (E) Color map representing the distances of normal voxels to the nearby emphysematous regions, from 1 to 5 mm. Red represents emphysema regions, labeled as 0 mm in the color scale. CT = computed tomography.

FEV₁, after adjustment for age, race, sex, body mass index (BMI), current smoking status, pack-years of smoking, and CT scanner protocol, as well as baseline FEV₁ and CT emphysema, gas trapping, and WA%. To test for association between spatial distributions of normal voxels in relation to emphysematous voxels, multivariable regression analysis was performed to find independent associations between change in FEV₁ and mean Jacobian determinant of MAL in 1-mm incremental distance from emphysematous voxels. No adjustments were made for multiple comparisons. All analyses were performed using Statistical Package for the Social Sciences (SPSS 22.0; SPSS Inc., Chicago, IL) and R statistical software version 3.2.

Results

Subject Characteristics

Baseline data for 680 participants with complete CT data are reported in Table 1 (see Figure E1). The mean (SD) age was 63.0 (8.4), 305 (44.9%) were female, and 167 (24.6%) were of African American race (see Table E1). A total of 256 (37.6%) were current smokers, and the average smoking pack-years was 49.8 (23.9). Participants encompassed the spectrum of disease severity with 120 (17.6%), 308 (45.3%), 190 (27.9%), and 62 (9.1%) having GOLD stages 1–4, respectively. Participants were followed for a median duration of 63 months (interquartile range, 60–66). The mean (SD) rate of decline in FEV₁ was 39.0 (58.6) ml/yr. Those with GOLD grade 1 had the most rapid rate of decline, 54.3 (61.2)

ml/yr. The rate of FEV₁ decline was slower with increasing GOLD grades: 45.6 (63.9), 28.8 (48.5), and 8.0 (33.3) for GOLD grades 2–4, respectively (trend test for grades 1–4; $P < 0.001$). Figure 2A shows that with increasing disease severity, there was progressive increase in CT emphysema and a decrease in the percentage of normal voxels.

Mechanics of Lung Parenchyma and Lung Function

Figure 2B shows that there was a progressive decrease in the mean Jacobian determinant of voxels with emphysema with increasing GOLD grade ($P < 0.001$ for overall trend and between group differences). Notably, there was also a similar decrease in the mean Jacobian determinant of normal voxels with increasing disease severity ($P < 0.001$). The mean Jacobian determinant of the entire lung was associated with FEV₁ on univariate analysis (regression coefficient $\beta = 1.063$; 95% confidence interval [CI], 0.834–1.291; $P < 0.001$) but not after adjustment for age, race, sex, BMI, current smoking status, pack-years of smoking, CT scanner protocol, CT emphysema, CT gas trapping, and WA% (adjusted $\beta = 0.021$; 95% CI, -0.171 to 0.213 ; $P = 0.830$).

To test our hypothesis of emphysematous voxels affecting the mechanics of normal voxels with the assumption that a greater number of emphysematous areas would result in more heterogeneous regional mechanics, we tested the association between the CV of Jacobian determinant and FEV₁. CV of Jacobian determinant for the entire lung,

including both emphysematous and normal voxels, was associated with FEV₁ on univariate and multivariable analyses, after adjustment for age, race, sex, BMI, current smoking status, pack-years of smoking, CT scanner protocol, CT emphysema, CT gas trapping, and WA% (adjusted $\beta = 0.821$; 95% CI, 0.364 to 1.278; $P < 0.001$), consistent with observations with progressive GOLD stage (Table 1). The CV of Jacobian determinant for normal voxels was also associated with FEV₁ on multivariable analyses (adjusted $\beta = 0.010$; 95% CI, 0.005–0.014; $P < 0.001$). This association was mainly seen in participants with GOLD stages 1 and 2, and not in GOLD stages 3 and 4 (see Table E2).

Spatial Relationship of Normal Voxels and FEV₁ Change

In predicting FEV₁ change, the CV of Jacobian determinant for the entire lung did not perform as well (adjusted $\beta = -38.083$; 95% CI, -91.384 to 15.218 ; $P = 0.161$) after adjustment for the previously mentioned variables and baseline FEV₁ (see Table E3). The CV of Jacobian determinant of normal voxels also did not predict lung function change (adjusted $\beta = -0.316$; 95% CI, -0.846 to 0.214 ; $P = 0.242$).

To improve the anatomic localization and clinical applicability of these mechanistic relationships between heterogeneity of lung mechanics and FEV₁ change, we examined the spatial distribution of normal voxels in relationship to emphysematous voxels. The mean percentage of voxels within 1 mm (MAL₁), 2 mm (MAL₂), and 3 mm (MAL₃) of emphysematous voxels was

Table 1. Univariate and Multivariable Associations with FEV₁

Parameter	Univariate Regression		Multivariable Regression	
	Regression Coefficient β (95% CI)	P Value	Regression Coefficient β (95% CI)	P Value
Age, yr	−0.017 (−0.024 to −0.011)	<0.001	−0.017 (−0.022 to −0.012)	<0.001
African American race	−0.100 (−0.230 to 0.030)	0.132	−0.212 (−0.302 to −0.123)	<0.001
Female sex	−0.597 (−0.701 to −0.494)	<0.001	−0.570 (−0.644 to −0.496)	<0.001
BMI, kg/m ²	−0.001 (−0.011 to 0.009)	0.888	−0.016 (−0.024 to −0.009)	<0.001
Smoking pack-years	−0.002 (−0.004 to 0.001)	0.201	−0.001 (−0.125 to 0.001)	0.701
Current smoker	0.276 (0.162 to 0.390)	<0.001	−0.033 (−0.125 to 0.058)	0.473
CT scanner type	−0.144 (−0.306 to 0.016)	0.078	0.117 (0.011 to 0.222)	0.029
CT emphysema, %	−0.027 (−0.031 to −0.022)	<0.001	−0.015 (−0.020 to −0.009)	<0.001
CT gas trapping, %	−0.019 (−0.022 to −0.017)	<0.001	−0.012 (−0.016 to −0.009)	<0.001
Segmental airway wall area, %	−0.081 (−0.099 to −0.064)	<0.001	−0.066 (−0.079 to −0.052)	<0.001
CV of Jacobian determinant, whole lung	3.412 (2.658 to 3.626)	<0.001	0.821 (0.364 to 1.278)	<0.001

Definition of abbreviations: BMI = body mass index; CI = confidence interval; CT = computed tomography; CV = coefficient of variation. Adjusted $R^2 = 0.61$.

Figure 2. Comparison of lung density and mechanics by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage for emphysematous and normal voxels. (A) With increasing severity of chronic obstructive pulmonary disease by GOLD grade, the percentage of voxels of the lung parenchyma with density less than -950 Hounsfield units (computed tomography emphysema) increases, whereas the number of normal voxels progressively decreases. (B) With progressive disease severity the mean Jacobian determinant, a measure of regional lung expansion, of the emphysematous voxels progressively decreases. Of note, the mean Jacobian determinant of the normal voxels also decreases with progressive GOLD grade. COPD = chronic obstructive pulmonary disease; CT = computed tomography.

17.1% (8.2%), 35.4% (13.9%), and 52.8% (15.9%), respectively. After adjustment for age, race, sex, BMI, current smoking status, pack-years of smoking, baseline FEV₁, CT scanner protocol, CT emphysema, CT gas trapping, and WA%, the mean Jacobian determinant of voxels within MAL₁ was significantly associated with FEV₁ change (adjusted $\beta = -21.985$; 95% CI, -43.791 to -0.179 ; $P = 0.048$). Similar relationships were seen for the mean Jacobian determinant of normal voxels within MAL₂ (adjusted $\beta = -22.243$; 95% CI, -44.317 to -0.169 ; $P = 0.048$). However, this relationship was no longer significant for voxels within MAL₃ and beyond (Figure 3). The spatial relationship held true for severe

emphysema (less than -950 HU) but not for milder emphysema (less than -910 HU) (see Table E4). To test whether MAL areas were influenced by lung densities borderline for emphysema, we converted HU to lung mass (g/ml) and found that there was no difference in lung density of each MAL area going from MAL 1 through 3 (see Table E5) (18).

To understand the significance of MAL₂ and its implications for lung function change in earlier disease stages, we also examined the rate of change of FEV₁ for varying levels of MAL₂ in GOLD grades 1 and 2 for whom the mean change of FEV₁ was -54.3 (61.2) ml. For participants at or above the median MAL₂ (36.9%), the mean decline in FEV₁ was 56.4 (68.0) ml/yr

versus 43.2 (59.9) ml/yr for those below the median ($P = 0.044$). For participants with greater than or equal to 75th percentile of MAL₂ (47.2%), the mean decline in FEV₁ was 65.3 (75.7) ml/yr compared with those below the 75th percentile (44.9 [60.2]; $P = 0.039$).

Discussion

We demonstrated that in participants with emphysema, normal-appearing lung regions on CT have abnormal regional expansion, and that there is a spatial relationship between areas of emphysema and abnormal lung mechanics resulting in a penumbra of

Figure 3. Spatial mapping of emphysema and surrounding normal areas depicting relative contributions of mechanically affected lung to FEV₁ change. Graphic of a hypothetical central emphysematous area and surrounding normal voxels. β represents adjusted regression coefficient for mean Jacobian determinant for each 1-mm incremental distance of normal voxels from emphysematous voxels. Computed tomography (CT) emphysema was defined as percentage of voxels less than −950 Hounsfield units (HU). All models for predicting FEV₁ change were adjusted for age, race, sex, body mass index, smoking pack-years, current smoking status, FEV₁ at baseline, CT emphysema, CT gas trapping, segmental wall area %, and CT scanner protocol. *Significant at $P < 0.05$.

MAL. In addition, we showed that quantifying the amount of MAL can independently predict lung function change over time.

Our results expand on previous preclinical studies that examined the relationship between mechanical stress and remodeling of lung parenchyma (9, 11, 13, 19). Cyclical stretching of the alveolar walls during respiration in the milieu of higher levels of degradative enzymes, as seen in emphysema, is associated with alveolar wall destruction seen on electron microscopy (19, 20). The extracellular matrix of the lung is constantly subject to transpulmonary pressure (21), and to intermittent increases during tidal breathing. The degree of pressure exposure is higher during bouts of coughing and exacerbations. In emphysematous areas, where the

extracellular matrix is already damaged, these pressure changes can cause sequential destruction of surrounding alveolar walls resulting in creation of fewer but larger clusters of emphysematous areas with disease progression (22). These findings are consistent with the zipper network model proposed for the failure of the extracellular matrix over time, wherein with decreasing number of fibrils, the remaining fibrils become exposed to progressively more pressure load and stretch and hence are more likely to rupture (12, 22). Here, we demonstrate the impact of emphysematous voxels on the regional expansion of surrounding voxels noninvasively in human subjects, and extend the findings of previous pathobiologic studies. This “penumbra” of MAL likely represents areas of

“lung at risk” for emphysema progression. Although we did not match images on follow-up scans voxel by voxel, we showed that these areas of at-risk lung, when quantified, independently predict lung function decline over time.

It follows that the effects of emphysema on surrounding lung are likely to be greater in mild to moderate emphysema than in more severe emphysema where the alveolar breaks tend to coalesce and progressively lesser number of surrounding normal alveoli are exposed to the effects of emphysematous regions (23). Indeed, we found that the percentage of voxels in MAL₂ decreased with progressively increasing GOLD grade. It is also possible that this effect is caused by lesser amount of remaining normal lung. A greater amount of emphysema can result in a decline in transpulmonary pressure as the lung matrix weakens, which in turn can result in reduced regional mechanical forces. In either case, these findings support the faster rate of lung function decline seen in the earlier phases of the disease reported in several large studies (15, 24–26).

Previous CT studies have shown that the presence and severity of emphysema on baseline scans predict lung function decline over time (4, 27). Indirect estimates of small airways disease are also associated with lung function change (15). These, however, represent established disease and do not inform about structural disease progression. Whether the at-risk lung can be modulated remains to be tested in future studies. Our results suggest that MAL₂ offers new information beyond that offered by previous CT metrics, and may serve as a CT-based biomarker of lung function decline in COPD. Although we calculated Jacobian metrics to mechanistically assess the influence of emphysematous areas on surrounding voxels, MAL₂ is based on spatial distribution of normal voxels and hence is an easily calculated measure on inspiratory scans.

The main strength of our study is that we included participants across a range of severity of disease in a well-characterized cohort with rigorous CT and spirometry quality control. Our study also had some limitations. Lung function measurements were made at two

time points separated by 5 years; however, the rate of change of lung function is consistent with other large studies and the within-person variability is likely reduced by the large sample size (4, 15, 28). We analyzed data from the first 847 GOLD 1–4 subjects who returned for follow up, and it is possible that this introduces a healthy survivor selection bias. We did not adjust FEV₁ decline for medication usage but no existing pharmacologic therapy has been unequivocally shown to alter lung function decline. CT image acquisition was not spirometrically gated but all participants were carefully coached to full inspiration and end expiration. We acknowledge that the *P* values were just below the 0.05 threshold, and no

corrections were made for multiple comparisons.

Finally, we used the less than −950 HU density threshold to define severe emphysema. Although it is possible that the penumbra effect could be caused by milder surrounding emphysema defined using lower thresholds, our models did not hold true using a −910 HU for mild emphysema, suggesting that MAL is a function of more severe emphysema. We also found that the lung density of MAL₁ through MAL₃ was not different, suggesting our results were not driven by changes in lung density in the areas surrounding emphysematous regions. In addition, although the use of other thresholds to define less severe emphysema might influence results, we were interested in the

effects of severe emphysema for which −950 HU is the most accepted threshold and is validated by microscopy (29).

Conclusions

Our findings suggest that areas of normal-appearing lung are mechanically influenced by emphysematous areas, and these regions of lung at risk are associated with lung function decline, thus providing a novel biomarker for disease progression in COPD that is measurable on clinical CT scans. More studies are needed to confirm these findings and to determine whether the lung at risk represents a target for interventions. ■

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

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