Original Investigation

Lung Mass in Smokers

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Rationale and Objective: Emphysema is characterized by airspace dilation, inflammation, and irregular deposition of elastin and collagen in the interstitium. Computed tomographic studies have reported that lung mass (LM) may be increased in smokers, a finding attributed to inflammatory and parenchymal remodeling processes observed on histopathology. We sought to examine the epidemiologic and clinical associations of LM in smokers.

Materials and Methods: Baseline epidemiologic, clinical, and computed tomography (CT) data (n = 8156) from smokers enrolled into the COPDGene Study were analyzed. LM was calculated from the CT scan. Changes in lung function at 5 years' follow-up were available from 1623 subjects. Regression analysis was performed to assess for associations of LM with forced expiratory volume in 1 second (FEV_1) and FEV_1 decline.

Results: Subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 chronic obstructive pulmonary disease had greater LM than either smokers with normal lung function or those with GOLD 2–4 chronic obstructive pulmonary disease ($P < 0.001$ for both comparisons). LM was predictive of the rate of the decline in FEV_1 (decline per 100 g, -4.7 ± 1.7 mL/y, $P = 0.006$).

Conclusions: Our cross-sectional data suggest the presence of a biphasic radiological remodeling process in smokers: the presence of such nonlinearity must be accounted for in longitudinal computed tomographic studies. Baseline LM predicts the decline in lung function.

Key Words: Lung mass; smoking; CT scan; COPD; emphysema.

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INTRODUCTION

Emphysema is defined as an abnormal, permanent dilation of the distal airspaces (1). The development and progression of this pathologic process are associated with a decline in lung function and progressive clinical impairment (2). Spirometric measures of lung function have been the benchmark for monitoring progression of disease and response to therapeutic intervention, but such investigations lack sensitivity and require large cohorts followed over relatively long periods of time (3). For these reasons, computed tomographic imaging of the chest is increasingly being leveraged as a source of intermediate study end points to objectively assess response to treatment (4–6).

Densitometric measures of the lung parenchyma to detect and quantify emphysema have been utilized in cross-sectional investigations for almost 30 years (7–9), including the percent low-attenuation area (%LAA—those regions of the lung less than a select attenuation value) and the percentage of lung volume less than the 10th or 15th percentile (8,10). Each of these measures may have relative advantages when considering disease severity and progression (11) but are all focused on the low-attenuation values of the lung histogram, the tail that may be most sensitive for the detection of airspace dilation. This may limit the ability of such metrics to fully assess the remodeling process characteristic of chronic obstructive pulmonary disease (COPD).

Prior histologic work by Vlahovic et al. demonstrated that airspace dilation in emphysema was also accompanied by inflammation and the deposition of excess elastin and collagen (12). The mean degree of airspace enlargement was directly related to interstitial thickness. Additional computed tomography (CT)-based work suggests that macroscopic emphysema is not just an absence of tissue. In their series of 40 subjects, Guenard et al. reported that 22 of the 24 patients with emphysema had normal or even increased lung mass (LM) (13). These previous studies prompted us to more comprehensively explore the significance of LM in smokers where we hypothesized that such measures would be highly clinically relevant even after adjustment for CT-based estimates of emphysema. To do this, we examined quantitative measures of emphysema and LM in CT scans obtained as part of the COPDGene Study (14).

MATERIALS AND METHODS

The COPDGene Study has been described in detail previously (14). Approximately 10,300 non-Hispanic White and African-American aged 45–80 years were recruited for the purpose of identifying genetic and epidemiologic predictors of the disease (thereafter referred to as the baseline cohort). At baseline, subjects underwent detailed characterization including volumetric inspiratory CT scans of the chest, questionnaires, and spirometric measures of lung function. Subjects with active lung diseases other than asthma, emphysema, or COPD were excluded. The COPDGene Study was approved by the institutional review board of each participating center, and all subjects provided written informed consent.

COPDGene subjects returned for a 5-year interval visit to repeat the characterization performed at baseline. The first 2000 data sets of smokers who returned to the second visit were the basis for the decline in lung function analysis using their clinical and CT data from their baseline visit.

Spirometric Measurements and COPD Definition

Spirometric measures of lung function including forced expiratory lung volume in 1 second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio were performed using the Easy-One spirometer (ndd Medical Technologies Inc., Andover, MA). Testing was performed before and after the administration of a short-acting inhaled bronchodilator (albuterol) per American Thoracic Society recommendations, and results were expressed as a percent of predicted values (15,16). Subjects were then classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of disease severity (17). Smokers with no evidence of spirometric obstruction (FEV_1/FVC > 0.7) were categorized as being "at risk" for the development of COPD, whereas those with an FEV_1/FVC <0.7 were categorized has having COPD. In our investigation, never-smoking subjects and smokers with a proportionally reduced FEV_1 and FVC with preserved ratio were excluded from analysis (18).

Clinical Assessment

Demographics and clinical demographic data including smoking history and acute respiratory disease events were obtained with standardized questionnaires, which are available at www.COPDGene.org. Acute respiratory disease episodes were defined as an increase of respiratory symptoms including cough, sputum production, and dyspnea in smokers with and without COPD. The episodes were counted if the subject had an episode lasting 48 hours or more and associated with antibiotic or corticosteroid use (19).

CT Assessment

Volumetric CT scans of the chest were performed at both maximal inflation and relaxed exhalation (14). Baseline inspiratory CT scans were used in this analysis. Images were acquired with the following CT protocol: for General Electric (GE) LightSpeed-16, GE VCT-64 (General Electric Healthcare, Chicago, IL), Siemens Sensation-16 and -64 (Siemens Healthineers, Erlangen, Germany), and Philips 40- and 60-slice scanners (Philips Healthcare Denver, CO) with 120 kVp, 200 mAs, and 0.5-second rotation time. Images were reconstructed using a standard algorithm at 0.625-mm slice thickness and 0.625-mm intervals for GE scanners; using a B31f algorithm at 0.625- (Sensation-16) or 0.75-mm slice thickness and 0.5-mm intervals for Siemens scanners; and using a B algorithm at 0.9-mm slice thickness and 0.45-mm intervals for Philips scanners (20). Densitometric assessments of the lung parenchyma were performed on the inspiratory scans using in-house software. Attenuation areas thought to reflect emphysematous destruction of the lung parenchyma were defined as the percent of lung attenuation areas less than −950 HU (%LAA-950). LM was calculated on a voxel-by-voxel basis as described and validated previously (21,22). Briefly, we used the following equation to calculate LM:

$$\text{Lung mass (g)} = \frac{\text{HU} + 1024}{1024} * \text{Voxel volume} * \text{No of voxels}$$

Statistical Analysis

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Data were presented as means ± standard deviation or median (interquartile range) for continuous variables according to their distribution type and as frequency (%) for categorical variables. All references to LM in this article pertain to measures obtained from the baseline CT scans. Comparisons of LM and %LAA-950 across GOLD groups were performed using analysis of the variance (GLM procedure of SAS). Between-group comparisons were carried out using appropriate contrast statements as well as an interaction term between GOLD stage and current smoking status. The latter was done to test differences in LM by smoking status across disease stages. In subjects with COPD, multivariable linear regression models were used to assess the relationship between LM and both baseline FEV_1