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Original Research

COPD

CT Metrics of Airway Disease and Emphysema in Severe COPD

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Background: **CT scan measures of emphysema and airway disease have been correlated with lung function in cohorts of subjects with a range of COPD severity. The contribution of CT scan-assessed airway disease to objective measures of lung function and respiratory symptoms such as dyspnea in severe emphysema is less clear.**

Methods: **Using data from 338 subjects in the National Emphysema Treatment Trial (NETT) Genetics Ancillary Study, densitometric measures of emphysema using a threshold of −950 Hounsfield units (%LAA-950) and airway wall phenotypes of the wall thickness (WT) and the square root of wall area (SRWA) of a 10-mm luminal perimeter airway were calculated for each subject. Linear regression analysis was performed for outcome variables FEV_1 and percent predicted value of FEV_1 with CT scan measures of emphysema and airway disease.**

Results: **In univariate analysis, there were significant negative correlations between %LAA-950 and both the WT ($r = -0.28$, $p = 0.0001$) and SRWA ($r = -0.19$, $p = 0.0008$). Airway wall thickness was weakly but significantly correlated with postbronchodilator FEV_1% predicted ($R = -0.12$, $p = 0.02$). Multivariate analysis showed significant associations between either WT or SRWA ($\beta = -5.2$, $p = 0.009$; $\beta = -2.6$, $p = 0.008$, respectively) and %LAA-950 ($\beta = -10.6$, $p = 0.03$) with the postbronchodilator FEV_1% predicted. Male subjects exhibited significantly thicker airway wall phenotypes ($p = 0.007$ for WT and $p = 0.0006$ for SRWA).**

Conclusions: **Airway disease and emphysema detected by CT scanning are inversely related in patients with severe COPD. Airway wall phenotypes were influenced by gender and associated with lung function in subjects with severe emphysema.** ***(CHEST 2009; 136:396–404)***

Abbreviations: BMI = body mass index; %LAA = percent emphysema; %LAA-950 = percent emphysema at a threshold of 950 Hounsfield units; NETT = National Emphysema Treatment Trial; Pi10-mm = 10-mm luminal perimeter; SRWA = square root wall area; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire; WT = wall thickness

COPD is characterized by incompletely reversible expiratory airflow obstruction[1] related to pathologic changes found in both the lung parenchyma and airways.[2] CT scanning is a minimally invasive tool employed to characterize these structural changes *in vivo*[3] and has been demonstrated repeatedly to be correlated with measures of airflow obstruction.[4–7] CT imaging has also been employed to objectively classify an individual as having either emphysema or airway-predominant disease,[8–10] and there is some suggestion that a subject's relative burden of airway and airspace disease may not be the result of totally independent processes.[11]

The National Emphysema Treatment Trial (NETT) consisted of subjects with severe emphysema who were randomly assigned to receive either lung volume reduction surgery or optimal medical therapy. At the time of study randomization, a CT scan of the chest was obtained in addition to standard measures of lung function and assessments of dyspnea. In the NETT cohort, some of the relationships between emphysema, health status, and lung function correlation have been reported previously,[7,12] but quantitative airway phenotypes have not been investigated. Using CT-based measures of airway disease, we could assess the epi-

demiologic associations between CT phenotypes and clinical metrics of disease, including physiologic and functional measures as well as frequency of exacerbations.

Recently, Patel and colleagues[11] reported that while there were independent functional correlations between both emphysema and airway disease with FEV_1, there was a weak but statistically significant negative correlation between measures of these two disease processes. Using the NETT data, we sought to examine the functional contribution of CT scan measures of emphysema and airway disease to clinical metrics of disease and the frequency of acute exacerbations of COPD. In addition, the emphysema and airway disease measurements made by CT scanning could be examined to determine whether the inverse correlation previously reported between these two metrics could be replicated in a cohort of subjects selected for having severe bilateral emphysema with presumed parenchymal predominant disease.

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*A list of members and participants in the National Emphysema Treatment Trial (NETT) is located in the Appendix.

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Materials and Methods

Clinical Characterization of Study Subjects

The current analysis included 338 non-Hispanic, white subjects from the Genetics Ancillary Study of NETT.[13] Selection of this cohort of subjects was based on CT scan availability and subsequent intended correlations of genetic information and CT measures of disease. Subjects enrolled in NETT had CT scan evidence of severe emphysematous destruction of the lung parenchyma and an FEV_1 of ≤ 45% predicted.[13] Spirometry was performed according to American Thoracic Society standards[14] before and after albuterol administration. A subject's bronchodilator response was calculated as the difference between their FEV_1 prior to and after the administration of two puffs of albuterol (180 μg total). This value was expressed as a percent of a subject's predicted FEV_1.

Clinical assessment included dyspnea quantified by using the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ), a validated questionnaire assessing symptoms of breathlessness[15] and a 6-minute walking test. A modified BODE index was calculated for each subject as performed previously by using a subject's FEV_1 percent predicted, UCSD SOBQ, 6-minute walk distance, and body mass index (BMI).[16] Using the Centers for Medicare and Medicaid Services claims data, COPD exacerbations were defined as one or more COPD-related emergency visits or hospitalizations occurring from 1 year prior to study enrollment through the 3 years following randomization.[17,18] Finally, tobacco smoke exposure (pack-year history) was calculated as the average number of packs of cigarettes smoked per day multiplied by the number of years of smoking. The study was approved by institutional review boards at participating centers. All subjects provided written informed consent.

Quantitative CT Scan Analysis

CT images of the chest were acquired at full inspiration with a minimum of 200 mA (greater in large subjects) and reconstructed using a high spatial frequency (bone) algorithm with a 1- to 2-mm collimation at 20-mm intervals. Densitometric measures of emphysema were analyzed by using a software program (Pulmonary Analysis Software Suite; PASS; Iowa City, IA) at a threshold of −950 Hounsfield units as described previously[7,19] and reported as the percent emphysema (%LAA). Per this convention, subjects with greater %LAA were observed to have greater parenchymal destruction manifested as emphysema on their CT scan. Airway wall thickness (WT) and the square root of wall area (SRWA) were assessed by using a tool for airway morphometry and airway quantification (Airway Inspector; www.airwayinspector.org) at Brigham and Women's Hospital. Individual airways that appeared round on visual inspection were manually selected in the right and left upper lobes and right lower lobe. The full width at half-maximum method was used to measure the WT and SRWA of each airway. From these discrete measures, the WT and SRWA of a 10-mm luminal perimeter (Pi10-mm) airway was calculated.[11,20] In this way, a subject's CT scan burden of airway disease could be expressed as a single metric where larger-derived measures of the WT and SRWA of the Pi10-mm airway represented greater CT scan burdens of airway disease.

Statistical Analysis

The CT phenotypes tested included the percent emphysema (percent emphysema at a threshold of 950 Hounsfield units [%LAA-950]), WT, and SRWA of a derived Pi10-mm airway. For univariate analysis, Pearson correlation coefficients were calcu-

lated between CT scan phenotypes, and gender differences were evaluated using *t* tests. Multivariate analysis was performed by using linear regression models for post-bronchodilator therapy percent predicted values of FEV_1 adjusting for subject's weight, pack-years of smoking, and the clinical center at which study enrollment occurred. To assess the influence of CT scan measures of airway disease on COPD exacerbations, exacerbations were defined as one or more COPD-related emergency visits or hospitalizations by using Centers for Medicare and Medicaid Services claims data and analyzed adjusting for age, gender, FEV_1, pack-years of smoking, and surgery status. The influence of emphysema and airway WT in this dichotomized cohort was then assessed by using logistic regression. p Values of < 0.05 were considered statistically significant. Statistical analyses were performed by using a statistical software package (SAS; SAS Institute; Cary, NC).

Results

Epidemiologic Data With Quantitative CT Scan Correlations

The demographic characteristics of the study cohort are provided in Table 1. Three hundred thirty-eight subjects were included in this analysis with a mean pre- and post-FEV_1 of 25.0% and 28.2% predicted, respectively. The mean age of the cohort was 67.5 years and approximately 64% of the subjects were men. Densitometric measures of emphysema and CT scan measures of airway disease were available on 317 of the 338 subjects and within this group the mean percentage of emphysematous lung was 16.6. The mean WT and SRWA of the entire cohort were 1.53 mm and 4.6 mm^2, respectively.

Male subjects were found to have significantly thicker airway walls than female subjects by using either the WT ($p = 0.007$) or the SRWA ($p = 0.0006$) of a Pi10-mm airway (Table 2). BMI was inversely correlated with %LAA-950 ($R = -0.26$, $p < 0.0001$) [Fig 1] and directly related to both WT and SRWA ($R = 0.24$, $p < 0.0001$; and $R = 0.19$, $p = 0.0004$, respectively). In addition, when adjusted for gender, BMI remained a significant predictor of the SRWA ($p = 0.002$). Finally, tobacco pack-year history was modestly but significantly inversely correlated with a subject's burden of emphysema ($R = -0.12$, $p = 0.04$), but its effect on WT did not reach statistical significance ($R = 0.09$, $p = 0.09$; and $R = 0.09$, $p = 0.11$ for WT and SRWA, respectively).

Table 1—*Demographic Characteristics of the 338 Subjects in the NETT Genetics Ancillary Study*

Characteristics	Values
Age, yr	67.5 ± 6.0
Male gender, No. (%)	217 (64.2)
Pack-years tobacco	67.6 ± 30.8
Before bronchodilator FEV_1, % predicted	25.0 ± 6.6
After bronchodilator FEV_1, % predicted	28.2 ± 7.4
%LAA-950 (n = 317)	16.6 ± 11.0
WT, mm	1.53 ± 0.25
SRWA, mm^2	4.6 ± 0.5

Values are given as mean ± SD unless otherwise noted. Emphysema measurements were available in 317 subjects.

Table 2—*Airway WT and the SRWA of a Derived Pi10-mm Airway*

	Male	Female	p Value
WT, mm	1.56 ± 0.23	1.48 ± 0.27	0.007
SRWA, mm^2	4.66 ± 0.47	4.47 ± 0.54	0.0006
%LAA-950	0.17 ± 0.10	0.16 ± 0.12	0.81

Values are given as mean ± SD. Results are presented by gender.

Quantitative CT Scanning and Subject Symptoms and Function

There were no significant associations between measures of airway WT and a subject's 6-minute walk distance or modified BODE index; however, there were significant associations between emphysema severity and 6-min walk distance ($\beta = -438$, $p = 0.03$), and between emphysema severity and modified BODE index ($\beta = 2.3$, $p = 0.02$) after adjusting for pack-years of smoking and clinical center. Similarly, neither CT scan measures of emphysema nor airway disease were predictive of a subject's symptoms as assessed by their UCSD SOBQ. Finally, there was no association between COPD exacerbations and the WT, SRWA, or %LAA-950 ($p = 0.2$, $p = 0.5$, and $p = 0.5$, respectively).

In the cohort of 317 subjects in whom quantitative measures of both emphysema and airway disease were available, there were significant inverse correlations between %LAA-950 and both WT ($r = -0.28$, $p < 0.0001$) and SRWA ($r = -0.19$, $p = 0.0008$; Fig 2). Airway WT (WT $R = -0.12$, $p = 0.03$), but not the SRWA ($R = -0.09$, $p = 0.09$) or %LAA-950 ($R = -0.07$, $p = 0.19$), was significantly correlated with postbronchodilator FEV_1% predicted. After adjusting for subjects' weight, pack-year tobacco history, and clinical center at which the subjects were enrolled, association of WT with postbronchodilator FEV1% predicted remained statistically significant ($\beta = -5.2$, $p = 0.009$), and SRWA and %LAA-950 became statistically significant ($\beta = -2.6$, $p = 0.008$; $\beta = -10.6$, $p = 0.03$, respectively).

In a multivariate model including WT and %LAA-950 as well as weight, pack-years, and clinical center, both WT and %LAA-950 were significantly associated with lung function ($p = 0.01$ and $p = 0.01$, respectively) [Table 3]. Airway wall and emphysema

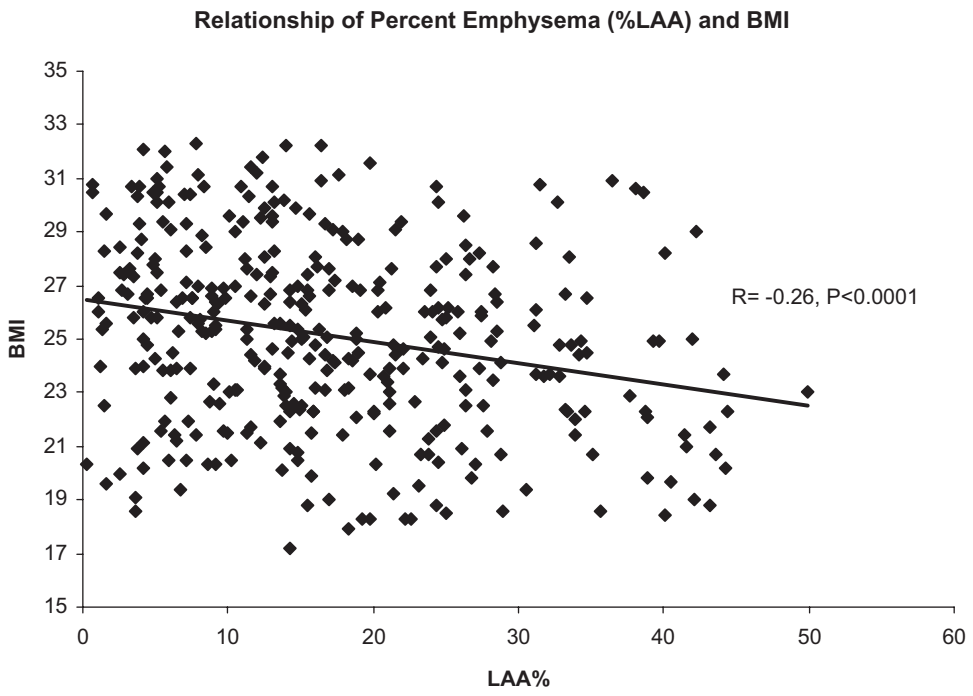

FIGURE 1. Relationship of %LAA and BMI.

phenotypes were not predictive of bronchodilator responsiveness ($p = 0.9$, 0.6, and 0.4 for WT, SRWA, and %LAA-950, respectively) after adjusting age, gender, pack-years of smoking, and clinical center. These findings were replicated by using the phase congruency method for airway segmentation[21] (data not shown) and as such are less likely to be an artifact of airway measurement technique.

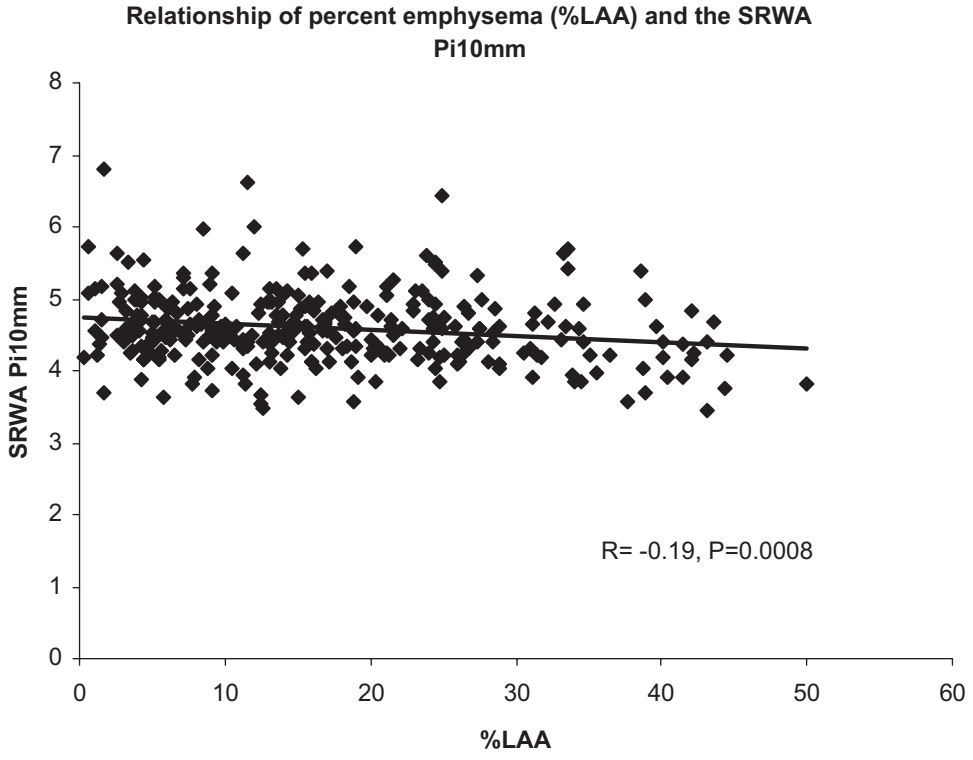

FIGURE 2. Relationship of the %LAA and SRWA Pi10 mm.

Table 3—*Association Analysis of Lung Function Revealed That Multivariate Models for Postbronchodilator FEV_1 % Predicted Was Associated With Either WT and LAA-950 (First Model) or the SRWA and LAA-950 (Second Model)*

First Model	β	p Value	Second Model	β	p Value
WT, mm	−5.2	0.01	SRWA, mm^2	−2.4	0.02
%LAA-950	−12.5	0.01	%LAA-950	−11.8	0.02

Both models were adjusted for weight, pack-years of smoking, and clinical center.

Discussion

Chest CT scanning has been increasingly used to define distinct imaging phenotypes in COPD,[4–7] including defining subjects as having either emphysema- or airway-predominant disease.[8–10] Interestingly, there has been a recent suggestion that a subject's relative burden of airway and airspace disease may in part be related.[11] Given these reports, we sought to examine the functional contribution of CT scan measures of airway disease in subjects with severe COPD and further determine if the findings of Patel and colleagues[11] could be replicated in a cohort of subjects with severe emphysema and presumed parenchymal predominant disease. Detailed assessments of imaging features with functional parameters in large cohorts of well-defined COPD patients have been scarce. The NETT Genetics Ancillary Study provided access to a large cohort of patients who were highly characterized clinically and physiologically and who underwent standardized CT imaging. In the current report, CT scan-based measures of both airway and airspace disease were performed and correlated to both functional and symptom-based indexes of disease. The derived measures of airway disease analyzed were both the WT and the SRWA of a theoretical Pi10-mm airway. We found that (1) airway wall phenotypes were significantly influenced by subject gender; (2) while the cohort exhibited a preponderance of emphysematous destruction of the lung parenchyma, measures of airway disease remained predictive of measures of lung function; (3) emphysema severity was predictive of 6-minute walk distance and modified BODE index, whereas airway wall imaging phenotypes were not correlated with other physiologic (6-min walk distance) or functional measures (dyspnea, health status); and (4) imaging was not able to segregate patients who subsequently did or did not experience COPD exacerbations.

A novel finding of our work is documentation that gender strongly influences CT scan measures of airway abnormality. Previous reports[12,22] have suggested that for an equal degree of airflow obstruction, men have significantly more emphysema than women. An initial examination of NETT patients suggested that women have proportionally more airway disease.[12] Based on these observations, and what is known about the correlation between proximal airway wall area and distal small airway disease, women were expected to have thicker proximal airway walls on CT scan.[21] Interestingly, in this subset of the NETT cohort, men had significantly thicker airway walls than women. The lack of standard prediction equations for airway wall measurements likely limits the interpretation of gender effects; it is possible that despite our finding of lower absolute airway WT measurements in women than men with COPD, that the percentage of predicted airway WT values could be greater in women.[12] For emphysema severity, we did not see any gender difference, possibly because of smaller sample size than in the initial report.[12]

Importantly, we noted an inverse relationship between emphysema severity and airway WT. This negative correlation has been reported previously in another recent report in the multicenter International COPD Genetics Network.[11] The etiology of this inverse relationship may be related to the pathobiology of disease, the mechanical interdependence of airway and airspace disease, or the lung volume at which the CT scan was performed. In the latter case, a loss of parenchymal tethering around the airway could lead to an observed increase in emphysema during inflation with minimal changes in the CT scan airway wall characteristics. Additional investigation is needed to clarify the reasons for the existence of such a relationship.

Our study also replicated reports of a significant association of airway phenotypes with lung function despite our cohort of parenchymal predominant disease subjects. The strength of these correlations was lower than previously reported[11]; however, the analysis of a cohort of subjects with severe emphysema may have attenuated the strength of this association. Similar correlations were not discovered between airway disease and either exercise capacity, bronchodilator response, or respiratory symptoms.

Access to highly characterized patients provided insight into imaging correlations. A subject's BMI significantly influenced airway WT and measures of emphysema[10,11,23] whereby subjects with lower BMIs tended to have more emphysema and less airway disease. Given the reproducibility of this finding, it is unlikely to be an artifact of this study population, and subject BMI may be a potential indication of the cachexia experienced by subjects with parenchymal predominant disease. Interestingly, pack-years of smoking was inversely correlated with %LAA-950 and tended to directly influence airway WT. While the latter observation is congruous

with the concept of chronic noxious stimuli leading to mural inflammation and airway remodeling, the inverse relationship between pack-years and emphysema is not as seemingly transparent. These findings may in part be due to the cohort under investigation. Only those subjects with severe COPD and emphysema on CT scan were included in the NETT. The homogeneity of such a study population may not provide the ideal cohort to examine the influences of smoking on CT scan metrics of disease. Alternatively, there may be a threshold of smoking exposure that increases the risk of emphysema, but increased smoking beyond that threshold may not further increase emphysema severity. This latter mechanism is purely speculative and would require further investigation within a cohort of subjects with a broader range of smoking history and functional impairment to substantiate.

Importantly, we did not record any impact of airway wall imaging phenotypes on other functional or symptomatic measures. In contrast, emphysema severity was associated with modified BODE and 6-minute walk distance. Association with modified BODE was shown in initial analysis with 1,053 NETT subjects.[12] Others have suggested that UCSD SOBQ is impaired to a greater extent in subjects with more CT emphysema.[10,24] In addition, others have suggested higher breathlessness in COPD subjects with greater emphysema.[8,11] The variance in findings could reflect methodological differences in imaging protocols or the nature of the patient population of our cohort, which comprised subjects preselected to exhibit severe emphysema.

CT scanning is becoming a widely used noninvasive tool to evaluate the lumenal narrowing and airway wall thickening associated with airway disease in subjects with COPD. There are several different investigational methods used to investigate and express these characteristic morphologic changes including the wall area percent and wall area of common airways across the cohort.[4,5] In cases such as ours where the CT images do not support such analysis, *ie*, have interval missing data such that common airways cannot be found in all subjects, derived measures of airway disease have been employed. The most standard of these is the SRWA of a 10-mm airway.[11] For the purposes of this investigation, we used discrete measures of both the airway WT and the SRWA to generate both the WT and SRWA of a Pi10-mm airway for each subject.

There were several limitations to this study. The NETT population comprised a cohort of patients with advanced COPD and a clinical and subjective imaging diagnosis of emphysema. Furthermore, we analyzed selected subjects in the ancillary genetics study rather than the whole NETT patient cohort, which may lead to selection bias. Specifically, the Genetics Ancillary Study consisted of subjects surviving several years after enrollment into the NETT, who were still alive at the time of study cohort formation. Survivor bias may therefore limit the conclusions that can be drawn from this investigation for the larger NETT cohort. Subjects were also recruited from multiple centers with different CT scanners that may affect the CT scan parameters.[25] Center effect may influence the associations despite our statistical adjustment for this effect. Despite this potential bias and multicenter recruitment effect, we observed weak but significant associations between FEV_1 and airway phenotypes in those subjects whose airway data were measured.

The results of this investigation demonstrate that even in a relatively homogeneous cohort of subjects with severe COPD, CT scan measures of emphysema and airway disease are independently predictive of expiratory airflow obstruction. In addition, in a cohort of subjects with presumed parenchymal predominant disease, CT scan measures of emphysema and airway disease are inversely correlated. Additional investigation is needed to determine if the observed inverse relationship between emphysema and airway disease has a histopathologic basis or is simply an artifact of imaging.

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Appendix

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