Gender Differences in the Severity of CT Emphysema in COPD*

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Background: **The hallmark of COPD is airflow obstruction, but this can develop on the basis of airway disease, emphysema, or both. There are gender differences in the natural history of COPD, and these may in part be explained by differences in the pathophysiology of airflow obstruction. We aimed to determine if there are gender differences in the severity of CT emphysema among COPD patients.**

Methods: **Current and former smokers enrolled in the National Lung Screening Trial (NLST) at the University of Alabama at Birmingham were recruited at the time of an annual screening CT examination. We recorded demographics and smoking history, and subjects performed spirometry. Subjects were classified into modified (prebronchodilator) Global Initiative for Chronic Obstructive Lung Disease stages, and their CT scans were analyzed to determine regional and total emphysema (defined as the percentage of low attenuation areas [LAA%]; < − 950 Hounsfield units). Differences between genders were examined, and univariate and multivariate predictors of LAA% were determined.**

Results: **A total of 396 subjects participated. Men had more regional and total CT emphysema at all stages of COPD than women (stage 0, 3.9% vs 2.4%, p = 0.001; stage I, 7.0% vs 3.7%, p = 0.015; stage II, 7.8% vs 5.5%, p = 0.063; stages III/IV, 15.8% vs 8.7%, p = 0.024). In multivariate regression analysis, only gender (p < 0.001) and FEV_1/FVC ratio (p < 0.001) predicted total LAA%.**

Conclusions: **At all stages of COPD severity, men have more CT emphysema than women. This difference in radiologic expression may in part explain gender differences in the presentation and natural history of COPD. The NLST (NCT00047385) is registered at www.clinicaltrials.gov.**

Registered at www.clinicaltrials.gov; no.NCT00047835

(CHEST 2007; 132:464–470)

Key words: COPD; CT scan pulmonary; physiology; pulmonary epidemiology

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAA = low attenuation areas; LAA% = percentage of low attenuation areas; NLST = National Lung Screening Trial

COPD has long been considered a disease of white men, but since 1980 mortality rates have risen faster in African Americans and women.[1] This is almost certainly explained in part by temporal changes in smoking habits, although some authors[2–6] have suggested that these groups may be more susceptible to the damaging effects of tobacco smoke. This concept of differential susceptibility remains controversial,[7] but it is becoming clear that there are important differences between men and

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This work was supported by a grant from the Morehouse/UAB Cancer Center Partnership.

The authors have no personal or financial conflicts of interest to declare.

Manuscript received April 6, 2007; revision accepted April 26, 2007.

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DOI: 10.1378/chest.07-0863

women in the presentation and course of COPD.[8–14] de Torres et al[6] reported that although women had better gas exchange and less comorbidity than men, they also had worse quality of life, more dyspnea and exacerbations, and less exercise tolerance. Studies of patients with moderate-to-severe COPD also suggest that women are less likely to benefit from long-term exercise training than men,[8] and have a higher risk of death while receiving long-term oxygen therapy.[9]

In recent years, it has also become apparent that COPD is a heterogeneous disease and that there are wide variations in the rate of decline of lung function, frequency of acute exacerbation, and degree of systemic involvement among sufferers.[15] These phenotypic differences are important because they may have independent genetic or environmental determinants and treatment implications.[15,16] Although airflow obstruction is the hallmark of COPD, this can develop on the basis of airways disease, emphysema, or both. These two processes can clearly coexist in a given patient but represent additional COPD phenotypes. It is possible that differences in the pathophysiology of airflow obstruction between the sexes could partly explain the gender differences in the natural history of COPD.

The development of multichannel CT scanning allows for the quantitative assessment of both the airway and parenchymal processes.[16,17] We hypothesized that there would be gender differences in the degree of CT emphysema among patients with COPD. Some of the results of this study have been previously reported in the form of an abstract.[18]

Materials and Methods

The study received approval from the National Cancer Institute as well as the University of Alabama at Birmingham and Partners Health Care Institutional Review Boards.

Patient Population

Subjects participating in the National Lung Screening Trial (NLST) at our institution were eligible for the study. The NLST is sponsored by the National Cancer Institute and was designed to compare annual chest radiographs with low-dose CT for the early detection of lung cancer.[19] The primary outcome of that study is lung cancer mortality, and approximately 50,000 subjects were recruited from 2002 to 2004. The NLST protocol calls for annual screening for 3 consecutive years and follow-up through 2009. Participants are men and women aged 55 to 74 years with a minimum 30–pack-year history of cigarette smoking. Exclusion criteria included prior lung cancer or pulmonary resection and acute respiratory infection requiring treatment with antibiotics in the previous 12 weeks. We recruited NLST participants assigned to the CT arm of the study at one of their three annual screenings.

Study Procedures

After undergoing their annual CT screening, subjects signed informed consent and their demographic and medical information was recorded. A smoking history was obtained, and cumulative pack-years of exposure were calculated. Subjects then performed spirometry according to American Thoracic Society standards,[20] and were classified in to modified (prebronchodilator) Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.[21] Subjects with an FEV_1/FVC ratio > 0.70 but reduced FEV_1 and FVC ($< 80\%$ of predicted) were classified as restricted. Predicted values for African Americans were adjusted by multiplying those for whites by 0.88.[22]

CT Analysis

NLST screening CT scans were obtained with a multichannel helical CT scanner at 120 kilovolt peak, 40 to 60 mA, and a 1-s scan time using 2.5-mm collimation and contiguous reconstructions. Quantitative densitometric analysis was performed, and areas of CT emphysema were defined as low attenuation areas (LAA) [<-950 Hounsfield units]. The percentage of LAA (LAA%) was then determined for the entire lung as well as for equal volumes of the upper, middle, and lower thirds of the lungs. This was done with free open-source software (3D Slicer; Brigham and Women's Hospital; Boston, MA) [www.slicer.org] using techniques developed in the Surgical Planning Laboratory at Brigham and Women's Hospital and described previously.[23]

Statistical Analysis

Differences in demographics, smoking history, lung function, and LAA% between men and women were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. Univariate and multivariate regression analysis was used to determine predictors of LAA%. Correlation coefficients were compared using Fisher R to Z transformation. Data are recorded as mean and SD or SE. Statistical software (SPSS, version 15.0; SPSS; Chicago, IL) was used for analysis.

Results

Demographics, smoking history, lung function, and CT emphysema (LAA%) for the 396 subjects who participated in the study are shown in Table 1. Enrollees were predominantly white and had a heavy smoking history. Although baseline demographic data and smoking history for the overall NLST population has not yet been published, subjects in

Table 1—*Subject Characteristics

Characteristics	Men (n = 246)	Women (n = 150)	p Value
Age, yr	62.9 ± 5.3	61.2 ± 4.6	0.001
White race, %	87.4	94.7	0.019
Pack-years, No.	57 ± 30	45 ± 24	< 0.001
Current smokers, %	53.2	60.0	0.23
FEV_1/FVC ratio	0.66 ± 0.11	0.68 ± 0.12	0.23
FEV_1, % predicted	72 ± 17	76 ± 20	0.062
LAA% upper third	7.6 ± 8.8	4.9 ± 6.8	0.002
LAA% middle third	6.2 ± 6.6	4.0 ± 4.1	< 0.001
LAA% lower third	6.4 ± 5.9	3.7 ± 4.1	< 0.001
LAA% total	6.7 ± 6.6	4.2 ± 4.4	< 0.001

*Data are reported as mean ± SD unless otherwise indicated.