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.**

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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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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.

the current study were comparable to those enrolled in the Lung Screening Study, which was conducted by the National Cancer Institute to determine the feasibility of performing a randomized trial of lung cancer screening in asymptomatic individuals.[24] The Lung Screening Study and NLST have similar inclusion and exclusion criteria. Mean pulmonary function results were consistent with GOLD stage II disease. There were significant gender differences in the population with men being older, less often white, and heavier smokers than women. In univariate analysis, men also had more CT emphysema than women in all lung regions and in total. These results were not different when LAA were defined using Hounsfield units < -910.

Table 2 displays the correlations between regional and total LAA% and measures of pulmonary function. All correlations were statistically significant. Although the correlations between LAA% and FEV_1/FVC were better than between LAA% and FEV_1 (percentage of predicted), these differences were not statistically significant. There were also no differences in the correlation coefficients between genders.

The univariate and multivariate regression analyses of predictors of total LAA% are shown in Table 3. In the univariate analysis, age, FEV_1 (percentage of predicted), FEV_1/FVC ratio, and gender significantly correlated with LAA%. However, only FEV_1/FVC ratio ($p < 0.001$) and gender ($p < 0.001$) remained significant when multivariate regression was performed. Gender and FEV_1/FVC ratio accounted for 37% of the variability in total LAA%. Similar results were found when only white subjects were included in the multivariate regression analysis.

Table 4 shows subject characteristics by GOLD stage including the restricted category. There were few differences in demographics, smoking history, and lung function between genders, except that men with stage 0 and 2 disease had heavier smoking histories than women, while women with stage 3 or 4 disease were younger than men. There were no differences in demographics, lung function, or total LAA% between men and women within the restricted category. Multivariate regression analysis within each GOLD stage confirmed that only gender and FEV_1/FVC ratio were predictive of total LAA% (analyses not shown).

As shown in Table 4 and in Figure 1, men had higher total LAA% than women across the GOLD stages, although this was not statistically significant for GOLD stage 2 subjects ($p = 0.063$). Men and women in the restricted category had similar degrees of CT emphysema. A test for linear trend between GOLD stages 0 and 3/4 was significant among women ($p < 0.05$) but not men.

Discussion

Emerging data strongly suggest that COPD is a heterogeneous disease with varying clinical phenotypes.[15] Although airflow limitation is the defining feature of COPD, there are many differences in disease expression including symptoms, systemic involvement, and radiologic features. These differing phenotypes may have various environmental or genetic determinants, including gender, and may have different pathophysiologic and treatment implications. We have found that at all levels of disease severity, current and former male smokers with COPD have more extensive CT emphysema than women. To our knowledge, this has not been previously reported. We believe that this gender difference in radiologic expression could represent an important difference in the pathophysiology of airflow obstruction between the sexes and that in part this may explain gender differences in the presentation and natural history of COPD.

Other investigators[25–27] have found that CT phenotypes correlate with clinical characteristics, pulmonary inflammation, and outcomes in patients with COPD. Fujimoto et al[25] studied 172 patients with stable COPD who underwent high-resolution CT and classified them into three categories based on visual analysis: little to no emphysema with or without bronchial wall thickening (airway phenotype), emphysema without bronchial wall thickening (emphysema phenotype), and emphysema with bronchial wall thickening (mixed phenotype). Subjects

Table 2—*Correlation Coefficients Between Regional and Total LAA% and Spirometry Measures

	All		Men		Women	
LAA%	FEV_1/FVC Ratio	FEV_1, % Predicted	FEV_1/FVC Ratio	FEV_1, % Predicted	FEV_1/FVC Ratio	FEV_1, % Predicted
Upper third	− 0.52	− 0.38	− 0.57	− 0.39	− 0.42	− 0.35
Middle third	− 0.57	− 0.43	− 0.61	− 0.42	− 0.53	− 0.48
Lower third	− 0.52	− 0.41	− 0.54	− 0.35	− 0.51	− 0.51
Total	− 0.58	− 0.44	− 0.62	− 0.42	− 0.55	− 0.49

*All correlations are statistically significant ($p < 0.001$).

Table 3—*Univariate and Multivariate Regression Analysis of Predictors of Total LAA%*

Variables	Univariate Analysis: Estimate (95% Confidence Interval)	Univariate Analysis: p Value	Multivariate Analysis: Estimate (95% Confidence Interval)	Multivariate Analysis: p Value
Age	0.24 (0.12 to 0.35)	< 0.001	0.09 (−0.01 to 0.18)	0.08
Male gender	2.51 (1.32 to 3.70)	< 0.001	2.18 (1.17 to 3.19)	< 0.001
White race	1.08 (−0.90 to 3.05)	0.29	1.12 (−0.47 to 2.71)	0.17
Pack-years	0.01 (−0.01 to 0.04)	0.18	− 0.01 (−0.03 to 0.01)	0.20
Current smoking	0.25 (−0.94 to 1.44)	0.68	− 0.15 (−1.13 to 0.82)	0.76
FEV_1, % predicted	− 0.13 (−0.16 to −0.10)	< 0.001	0.02 (−0.02 to 0.05)	0.39
FEV_1/FVC ratio	− 29.4 (−33.5 to −25.4)	< 0.001	− 30.2 (−35.8 to −24.7)	< 0.001

with the airway phenotype were more often never-smokers, had higher body mass index and diffusing capacity, less hyperinflation, and greater reversibility to bronchodilator than those with the emphysema phenotype. In that report,[25] no correlation between the severity of airflow limitation and the distribution of CT phenotypes was provided and there were no differences in the distribution of CT phenotypes based on gender. Boschetto et al[26] recently compared physiologic measures and sputum characteristics between COPD patients with significant emphysema (mean LAA, 27%; n = 11) and those without (mean LAA, 4.7%; n = 15). The study was too small to address gender differences, but subjects with more advanced emphysema had higher sputum levels of matrix metalloproteinase-9 and higher matrix metalloproteinase-9/tissue inhibitor of metalloproteinase ratios, suggesting more active pulmonary inflammation. In addition, emphysematous subjects had lower FEV_1 and diffusing capacities as well as higher BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity in COPD) scores and lower inspiratory capacity/total lung capacity ratios. The latter two findings suggest that emphysema may be a predictor of mortality; indeed, in an analysis of data from the National Emphysema Treatment Trial, Martinez et al[27] showed that a greater proportion of CT emphysema in the lower lung zones vs the upper predicts death in patients with severe airflow limitation.

Table 4—*Subject Characteristics by GOLD Stage*

Characteristics	Men	Women	p Value
Stage 0 (55 men, 54 women)			
Age, yr	61 ± 5	60 ± 5	0.24
Pack-yr, No.	46 ± 19	37 ± 20	0.01
FEV_1/FVC ratio	0.77 ± 0.05	0.77 ± 0.05	0.56
FEV_1, % predicted	92 ± 9	94 ± 9	0.23
LAA total, %	3.9 ± 2.5	2.4 ± 2.5	0.001
Stage 1 (33 men, 19 women)			
Age, yr	63 ± 5	61 ± 5	0.22
Pack-yr, No.	62 ± 37	49 ± 27	0.18
FEV_1/FVC ratio	0.64 ± 0.04	0.66 ± 0.04	0.21
FEV_1, % predicted	87 ± 6	89 ± 7	0.34
LAA total, %	7.0 ± 5.2	3.7 ± 3.1	0.015
Stage 2 (84 men, 32 women)			
Age, yr	63 ± 5	63 ± 4	0.78
Pack-yr, No.	61 ± 33	43 ± 15	0.01
FEV_1/FVC ratio	0.61 ± 0.07	0.61 ± 0.07	0.66
FEV_1, % predicted	64 ± 8	67 ± 8	0.10
LAA total, %	7.8 ± 6.0	5.5 ± 4.8	0.063
Stage 3 or 4 (22 men, 20 women)			
Age, yr	66 ± 6	61 ± 4	0.002
Pack-yr, No.	62 ± 31	59 ± 26	0.69
FEV_1/FVC ratio	0.44 ± 0.12	0.46 ± 0.09	0.74
FEV_1, % predicted	41 ± 7	41 ± 6	0.99
LAA total, %	15.8 ± 12.3	8.7 ± 5.8	0.024
Restricted (52 men, 25 women)			
Age, yr	63 ± 5	62 ± 5	0.34
Pack-yr, No.	55 ± 24	52 ± 31	0.68
FEV_1/FVC ratio	0.75 ± 0.04	0.75 ± 0.04	0.87
FEV_1, % predicted	70 ± 8	67 ± 7	0.17
LAA total, %	3.9 ± 3.0	3.2 ± 3.9	0.39

*Data are reported as mean ± SD.

Other reports have suggested that in fact there may be differences in the extent of airway disease and emphysema between genders and this may have implications for COPD management. As part of a lung cancer screening protocol in Japan, Wang et al[28] found that the prevalence of emphysema was higher in men than in women (5.0% vs 0.5%, $p < 0.01$) and that when present it was more severe among men. In both sexes, the rates of CT emphysema were quite low, but this likely reflects the fact that participants were aged 19 to 92 years and many were nonsmokers. In a study of 1,438 COPD patients by Tatsumi et al,[29] men were more likely than women to have an emphysema-predominant phenotype (LAA > 50%), while airway-predominant disease (LAA < 25%) was more common among women.[29] The airway phenotype was also more common among nonsmokers and more often accompanied by bronchodilator reversibility (35% vs 21%, $p < 0.01$), an elevated eosinophil count, and less overall lung function impair-

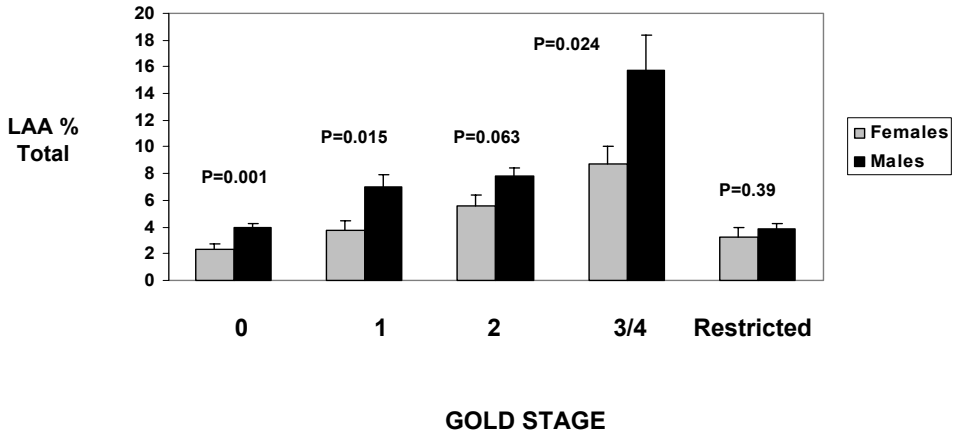

FIGURE 1. Gender differences in CT emphysema (LAA%) by GOLD stage. Shown is the mean total LAA% by GOLD stage including those with restrictive pulmonary function ($FEV_1/FVC > 0.70$ and $FEV_1 < 80\%$ of predicted). LAA% increased with GOLD stage in both men and women, but men had more emphysema regardless of COPD severity. There was no gender difference in LAA% in the restricted group. Error bars denote SE.

ment. Interpretation of these studies is significantly limited because emphysema was quantified visually and spirometry was not performed[28] or gender-specific lung function data not reported.[29] As a result, conclusions about gender differences in CT emphysema are confounded by the absence of information about disease severity. Kanner et al[10] has also reported that airways disease as measured by methacholine reactivity was more common among women in the Lung Health Study than among men and that this reflected the fact that their airway caliber was smaller. This methacholine reactivity was also more strongly related to the subsequent rate of lung function decline in women ($p < 0.0001$). In addition, women who were sustained quitters gained more lung function (percentage of predicted FEV_1) than men, suggesting that women may be more responsive to smoking cessation.[11] Smaller airway size in women may also place them at greater risk for airways disease because toxic particulates may be more likely to deposit prior to reaching the alveoli.[30]

The results of these prior studies and our report suggest that CT phenotypes do correlate with clinical characteristics in patients with COPD and that men are more likely to have emphysema-predominant CPD and women to have airway-predominant COPD. However, we are unaware of any prior report that has examined gender differences in the quantitative extent of emphysema (either radiographic or pathologic) based on COPD severity. Our results argue more strongly that the pathophysiology of COPD-associated airflow limitation may truly be different between men and women and that these differences manifest early in the development of the disease.

We found no correlation between pack-years of cigarette smoking and the severity of CT emphysema. This appears counterintuitive because cigarette smoking is clearly the major risk factor for the development of COPD; however, other investigators have reported the same result. Although Wang et al[28] found a distinct correlation between smoking and the prevalence of emphysema, indexes of smoke exposure did not correlate with the extent of CT abnormalities. Gillooly and Lamb[31] also reported no correlation between smoking habits and the extent of microscopic emphysema.

The advent of multichannel CT scanning has allowed for greater definition of both parenchymal and airway abnormalities in COPD.[16] Although effort has been made to correlate measurements of regional and total CT emphysema as well as airway abnormalities with pulmonary function, the correlations with spirometry are moderate at best as they were in our study.[17,32] Although these simple spirometric correlations have been disappointing, Cerveri et al[32] showed that a multivariate model of prebronchodilator and postbronchodilator physiologic measures is a better predictor of emphysema as measured by high-resolution CT scans explaining 71% of the variability in its extent. In addition, emerging data suggest that CT localization of emphysema can be used to predict the response to lung volume reduction surgery[33] and to help select candidates for the procedure.[34]

Our study has several limitations. First, only prebronchodilator spirometry was available, and as a result we were unable to stage COPD severity using postbronchodilator lung function as is recommended by the GOLD guidelines. Indeed, there is evidence

that between 20% and 30% of subjects meeting criteria for obstruction prebronchodilator will not meet these criteria after the administration of an inhaled bronchodilator.[35] However, this approach has been used by other investigators and prebronchodilator staging has been shown to predict COPD-related hospitalization and death.[36] It could be argued that the use of prebronchodilator spirometry may have also led to misclassification of the GOLD stage of women in the study. If women are truly more likely than men to have airway abnormalities, they may be more likely to respond to bronchodilators. As a result, prebronchodilator spirometry may overestimate the GOLD stage in women and artificially separate the difference in LAA% between genders. This phenomenon seems less likely, however, because preliminary results from a large randomized trial[37] of tiotropium in COPD suggest that women respond less well to bronchodilators than do men. Second, the observed gender differences in CT emphysema could also be the result of men having more emphysema even in the absence of smoking or COPD. This is unlikely because Gevenois et al[38] has shown that healthy nonsmoking men and women have comparable mean lung density.

In conclusion, these data argue that CT emphysema develops more quickly in men than in women and that smoking alone does not explain the discrepancy. It is possible that this gender difference in radiologic expression of COPD may in part explain the differences between men and women in the natural history of the disease. Gender differences in the pathophysiology and treatment of COPD warrant additional study.

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