

Sex Differences in Severe Pulmonary Emphysema

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Rationale: Limited data on sex differences in advanced COPD are available.

Objectives: To compare male and female emphysema patients with severe disease.

Methods: One thousand fifty-three patients (38.8% female) evaluated for lung volume reduction surgery as part of the National Emphysema Treatment Trial were analyzed.

Measurements and Main Results: Detailed clinical, physiological, and radiological assessment, including quantitation of emphysema severity and distribution from helical chest computed tomography, was completed. In a subgroup (n = 101), airway size and thickness was determined by histological analyses of resected tissue. Women were younger and exhibited a lower body mass index (BMI), shorter smoking history, less severe airflow obstruction, lower DL_{CO} and arterial PO₂, higher arterial PCO₂, shorter six-minute walk distance, and lower maximal wattage during oxygen-supplemented cycle ergometry. For a given FEV₁% predicted, age, number of pack-years, and proportion of emphysema, women experienced greater dyspnea, higher modified BODE, more depression, lower SF-36 mental component score, and lower quality of well-being. Overall emphysema was less severe in women, with the difference from men most evident in the outer peel of the lung. Females had thicker small airway walls relative to luminal perimeters.

Conclusions: In patients with severe COPD, women, relative to men, exhibit anatomically smaller airway lumens with disproportionately thicker airway walls, and emphysema that is less extensive and characterized by smaller hole size and less peripheral involvement.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Sex differences in chronic obstructive pulmonary disease are increasingly recognized.

What This Study Adds to the Field

In patients with severe COPD, women, relative to men, exhibit anatomically smaller airway lumens with disproportionately thicker airway walls, and emphysema that is less extensive and characterized by smaller hole size and less peripheral involvement.

Keywords: chronic obstructive pulmonary disease; emphysema; computed tomography; pulmonary function; gender

The prevalence and mortality of chronic obstructive pulmonary disease (COPD) in female smokers is rapidly increasing (1). Female smokers are more likely than men to report respiratory symptoms (2–4) and exhibit greater baseline airway responsiveness to methacholine (5). Indirect evidence suggests that women may be more predisposed to develop smoking-induced lung function impairment (4, 6, 7) and experience greater mortality (8). Despite these compelling data, COPD continues to be underdiagnosed in women (9), and research into sex differences in advanced COPD remains limited (4, 10, 11). Using carefully characterized patients from the National Emphysema Treatment Trial (NETT), we hypothesized that differences in disease expression in severe emphysema would be identified between males and females. Specifically, we sought to examine differences in the symptomatic, physiological, radiological, and histological expression of emphysema.

METHODS

Patient Selection

The study group consisted of 1,053 patients randomized at 17 NETT clinics (12) in whom baseline high resolution computed chest tomographs (HRCT) were available for analysis at the Imaging Analysis Center of the University of Iowa (*see below*). The design and methods of the trial have been detailed previously (12, 13); major enrollment criteria are enumerated in the online supplement.

Clinical Assessment

Demographic data and medical history were collected using standardized instruments. Health status was assessed using general and disease-specific instruments. Dyspnea was quantified using the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (14). Depression was assessed using the Beck Depression Inventory (15).

Physiological Testing

Patients underwent spirometry before and after albuterol administration, while plethysmographic lung volumes were measured after albuterol administration. Diffusing capacity and arterial blood gases were also measured. The protocol for 6-minute walk testing (6MWT) has been described (16). Maximal exercise capacity was measured using a cycle ergometer. A multidimensional index, the BODE, was modified using previously described methodology (mBODE) (17).

Diagnostic Imaging Studies

Emphysema severity and distribution was determined from chest computed tomography (CT) scans obtained at full inspiration. After segmenting and dividing the lung according to previously described protocols (18), images were analyzed using custom-built software, the Pulmonary Analysis Software Suite (PASS). The density histogram was plotted, with values less than -950 HU corresponding to severe emphysema and regions with values of -910 HU and -850 HU roughly equating to moderate and mild emphysema, respectively. The alpha value (inverse slope) was determined from the log-log relationship of hole size versus number of holes (19). Lungs with greater proportions of small lesions have a steep negative slope and a large alpha.

Histological Assessment

Lung tissue was available for analysis in 101 subjects from five centers (Baylor, Colorado, Michigan, Pittsburgh, and Temple). Previous reports have described the methods used to process the tissue and to estimate airways remodeling and luminal occlusion by inflammatory exudates containing mucus (20). We examined cross sections of airways < 2 mm in diameter. Maximal lumen area was calculated (18, 21). Wall thickness included the area between the epithelial luminal surface and the connective tissue at the outer limit of the adventitia. The fractional areas (V_v) taken up by epithelium, lamina propria, the smooth muscle itself, and the adventitia were also measured. The ratio of tissue area to basement membrane length was used to express the volume to surface (V/S) ratio or thickness of the airway wall and its compartments.

Statistical Analysis

Continuous data were compared using t tests. Multivariate linear regression models were used to assess the relationships between sex and dependent variables of FEV₁% predicted, mBODE, dyspnea, depression, health status scores, whole-lung emphysema, and whole-lung alpha. Potential confounders included age, number of pack-years, whole-lung emphysema proportions, and FEV₁% predicted (confounder excluded when it was the dependent variable in the model). mBODE or inspiratory capacity (IC)/TLC were also explored as confounders when appropriate. All sex comparisons of airway wall and its compartments were performed using a mixed hierarchical model, which accounted for the clustering of airway analysis within subjects (Proc Mixed, version 9.1; SAS, Cary, NC).

RESULTS

Patient Demographics and Baseline Physiology

Compared with males, female subjects were slightly younger, had a slightly lower mean Body Mass Index (BMI), and reported significantly shorter smoking histories and an older age at the time of smoking onset (Table 1). Women exhibited slightly less severe airflow obstruction but a similar TLC, slightly lower diffusing capacity (DL_{CO}), IC/TLC, Pa_{O₂}, and higher Pa_{CO₂}. The difference in Pa_{O₂} persisted when adjusted for differences in Pa_{CO₂} (difference -2.21 mm Hg; 95% confidence interval [95% CI], $-3.44, -0.98$; $P = 0.0004$). The 6MWT and maximal exercise

capacity were lower in women. Men exhibited slightly lower α_1 -antitrypsin levels than women (Table 1), although the distribution of α_1 genotypes was not different ($P = 0.44$, data not shown). In the cohort there were only 16 patients felt to be α_1 -deficient; in this group, only two were females.

After adjusting for age, pack-years of smoking, and whole-lung emphysema proportion, women showed a higher prebronchodilator FEV₁% predicted than men (mean FEV₁% predicted 2.98% greater; 95% CI, 2.19, 3.78; $P < 0.0001$). Although the results were not statistically confirmed when predicted values of Hankinson and coworkers (22) were substituted for those of Crapo and colleagues (23–25), the direction remained suggestive (mean FEV₁% predicted 0.69% greater; 95% CI, $-0.14, 1.51$; $P = 0.10$). All interactions involving sex and other predictors in the model were investigated; none were found to be significant. Results were similar when postbronchodilator FEV₁ was examined (data not shown). Lower DL_{CO} in females remained significant (-2.79% pred; 95% CI, $-3.99, -1.58$) after adjustment for whole lung emphysema proportion, age, and pack-years of smoking.

Breathlessness, Depression, and Health Status

Female patients noted greater breathlessness (UCSD SOBQ) and depression (Beck total score), and lower SF-36 mental component score (MCS) (Table 1). Increased breathlessness in women (average adjusted UCSD SOBQ score 5.03 higher; 95% CI, 2.57–7.49) remained significant ($P < 0.0001$) after adjusting for age, FEV₁% predicted, whole-lung emphysema proportion, and pack-years (Table 2). Results were similar when postbronchodilator FEV₁ was used in the models (data not shown), although they were less evident when the IC/TLC was included in the model (see Table E1 in the online supplement).

In separate multivariate models predicting total Beck score (Table 2) and SF-36 MCS (Table 2), significant interactions between age and sex were found after adjusting for FEV₁% predicted, whole-lung emphysema proportion, and pack-years. These sex interactions remained when the FEV₁ was replaced by the IC/TLC score or the mBODE (Tables E1 and E2). Based on these interaction analyses, our data suggest that women under the age of 79.2 years tended to have a higher total Beck score than men, but as age increased, the total Beck score tended to decrease more rapidly in women than in men (Figure 1A). Similarly, women under the age of 73.5 years tended to have a lower SF-36 MCS than men of the same age, with the disparity between sexes decreasing with age (Figure 1B). These strong sex interactions remained evident after adjustment for mBODE scores (Figure E1). No other interactions with sex were found to be significant in Table 2.

Few differences were noted between sexes in health status, as assessed by the SF-36 physical component score or the SGRQ, in either univariate or multivariate analyses (Table 2). In univariate analysis, QWB was marginally lower in women than men ($P = 0.05$). In the multivariate setting (Table 2), the statistical significance of the association of QWB with female sex increased after adjusting for confounders (on average females lower by 0.02; 95% CI, $-0.003, 0.036$ lower; $P = 0.02$). Results were quantitatively similar using both sets of predicted values for FEV₁. When postbronchodilator FEV₁ was used in modeling the association of QWB and sex, it became marginally significant (0.001; 95% CI, $-0.00001, 0.0002$; $P = 0.05$).

Radiographic Assessment of Emphysema Proportion and Distribution

The proportion of whole-lung emphysema in women was lower using a threshold that identifies moderate emphysema (-910 HU,

TABLE 1. BASELINE CHARACTERISTICS FOR PATIENTS WITH SEVERE EMPHYSEMA

Parameter	Men (n = 644) Mean (SD)	Women (n = 409) Mean (SD)	P Value
Demographics/Laboratory			
Age, yr	67.0 (6.2)	65.4 (6.1)	0.0001
BMI, kg/m ²	25.0 (3.7)	24.4 (4.2)	0.007
Pack-years	71.1 (32.3)	54.8 (24.2)	0.0001
Age at onset of smoking habit, yr	16.0 (3.7)	17.7 (3.9)	< 0.0001
α ₁ -antitrypsin, mg/dl	152.4 (36.0)	163.0 (37.5)	< 0.0001
Physiology*			
Pre BD FEV ₁ , ppd	22.7 (6.4)	25.6 (6.2)	0.0001
Post BD FEV ₁ , ppd	25.9 (7.1)	29.0 (6.6)	< 0.0001
(Post BD FEV ₁ -Pre BD FEV ₁)/Pre BD FEV ₁	0.15 (0.13)	0.15 (0.14)	0.50
Post BD FEV ₁ ppd -Pre BD FEV ₁ ppd	3.23 (2.80)	3.46 (3.15)	0.22
TLC, ppd	128.3 (13.9)	129.3 (14.8)	0.28
D _{LCO} , ppd	29.3 (10.0)	27.2 (9.0)	0.0005
6MWT, ft	1185.5 (322.5)	1076.7 (291.7)	0.0001
Maximum load, watts	43.0 (22.4)	26.2 (14.4)	< 0.0001
Pa _{o₂} , mm Hg	65.8 (10.13)	62.8 (10.30)	< 0.0001
Pa _{co₂} , mm Hg	42.2 (5.17)	43.3 (5.40)	0.0008
IC/TLC	0.23 (0.06)	0.21 (0.06)	< 0.0001
Symptoms and Health Status			
UCSD SOBQ	64.0 (18.9)	67.4 (18.8)	0.005
SF-36 PCS	28.4 (7.7)	28.5 (7.6)	0.92
SF-36 MCS	53.1 (10.8)	51.6 (10.8)	0.03
QWB	0.542 (0.120)	0.527 (0.127)	0.05
SGRQ overall score	56.4 (13.0)	56.2 (13.2)	0.79
Beck Total Score	8.7 (5.59)	10.4 (6.90)	0.0001
Multidimensional Index			
mBODE	5.27 (1.59)	5.72 (1.59)	< 0.0001
Imaging			
Whole lung emphysema proportion			
-950 HU threshold	0.16 (0.11)	0.15 (0.11)	0.07
-910 HU threshold	0.44 (0.12)	0.41 (0.12)	0.0001
Alpha			
-950 HU threshold	1.02 (0.20)	1.06 (0.24)	0.001
-910 HU threshold	0.71 (0.12)	0.74 (0.14)	0.01
Whole lung peel emphysema proportion at -950 HU	0.123 (0.091)	0.105 (0.086)	0.002
Whole lung core emphysema proportion at -950 HU	0.207 (0.128)	0.207 (0.138)	0.93

Definition of abbreviations: 6MWT = six minute walk test; BD = bronchodilator; BMI = body mass index; D_{LCO} = diffusing capacity for carbon monoxide; HU = Hounsfield Unit; IC = inspiratory capacity; maximum load = maximal exercise capacity measured on cycle ergometry while breathing 30% FiO₂; mBODE = modified BODE; MCS = mental component scale; Pa_{o₂} = room air resting Pa_{o₂} in mm Hg; Pa_{co₂} = room air resting Pa_{co₂} in mm Hg; ppd = percent predicted; PCS = physical component scale; QWB = quality of well-being; SF-36 = Short form 36 health survey; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

*Physiologic predicted values of Crapo and coworkers (23–25).

$P < 0.0001$), and marginally lower using a threshold for severe emphysema (-950 HU, $P = 0.07$) (Table 1). These associations were maintained in multivariate models (Table 3) (on average 3% less moderate emphysema; 95% CI, 1.4–4.6% less; $P = 0.0002$, on average 16.4% less severe emphysema; 95% CI, 0.2–30.5% less; $P = 0.02$). Postbronchodilator FEV₁ was significant when included in the model identifying severe emphysema (-950 HU) (-0.001 ; 95% CI, -0.002 , -0.0002 , $P = 0.01$), while other differences were unchanged. These results remained qualitatively similar when the FEV₁ was replaced by the IC/TLC (Table E3) and the mBODE (Table E4). Similarly, women exhibited significantly higher whole-lung alpha value using either emphysema threshold (Tables 1 and 3). No significant interactions of other covariates with sex were found in any of the multivariate models in Table 3. When the analyses were adjusted for IC/TLC (Table E3) and mBODE (Table E4) in place of FEV₁, the direction of these differences was similar.

Emphysema distribution also differed between sexes (Table 1). Women showed a similar proportion of emphysema in the core of the lung ($P = 0.93$) but a lower proportion in the peel ($P =$

0.002). Results were quantitatively similar using both sets of predicted values for FEV₁.

Histological Assessment

The small airways of the female lung had a reduced basement membrane length (PI) compared with male lungs, but only marginally lower total wall area (Table 4). This disparity resulted in clear sex differences ($P < 0.05$) in estimates of thickness obtained from the ratio of wall area/PI for the total wall and its epithelial and adventitial compartments.

DISCUSSION

This retrospective analysis of a large, prospectively studied cohort of patients with severe COPD enrolled in a clinical trial of lung volume reduction surgery documents sex-specific disparities in symptom severity, health status, and distribution of pathologic changes assessed using both radiological and histological techniques. For a given age, FEV₁% predicted, smoking history, and proportion of emphysema, women experienced greater dyspnea,

TABLE 2. MULTIVARIATE LINEAR REGRESSION MODELS PREDICTING THE mBODE, DYSPNEA, BECK DEPRESSION SCORES, AND HEALTH STATUS IN PATIENTS WITH SEVERE EMPHYSEMA (N = 1,053)

	Parameter Estimate	95% Confidence Interval	P Value
Modified BODE			
Intercept	5.69	(4.47, 6.90)	< 0.0001
Age	-0.02	(-0.04, -0.003)	0.02
Whole lung emphysema proportion, -910 HU	0.01	(0.005, 0.02)	0.002
Pack-years	0.002	(-0.001, 0.006)	0.19
Female sex	0.42	(0.20, 0.64)	0.0002
UCSD SOBQ			
Intercept	98.22	(84.8, 111.68)	< 0.0001
FEV ₁ , % predicted	-0.59	(-0.77, -0.41)	< 0.0001
Age, yr	-0.31	(-0.50, -0.13)	0.001
Whole lung emphysema proportion, -910 HU	-5.57	(-14.8, 3.68)	0.24
Pack-years	0.036	(-0.001, 0.07)	0.06
Female sex	5.03	(2.57, 7.49)	< 0.0001
Beck Total score			
Intercept	12.56	(7.18, 17.9)	< 0.0001
FEV ₁ , % predicted	-0.05	(-0.11, 0.01)	0.09
Age, yr	-0.07	(-0.15, 0.002)	0.06
Whole lung emphysema proportion, -910 HU	0.40	(-2.63, 3.43)	0.80
Pack-years	0.03	(0.02, 0.04)	< 0.0001
Female sex	11.09	(3.02, 19.2)	0.007
Age, yr · female sex	-0.14	(-0.26, -0.01)	0.03
SF-36 Physical component score			
Intercept	12.82	(7.27, 18.4)	< 0.0001
FEV ₁ , % predicted	0.06	(-0.01, 0.14)	0.11
Age, yr	0.20	(0.12, 0.28)	< 0.0001
Whole lung emphysema proportion, -910 HU	2.49	(-1.33, 6.30)	0.20
Pack-years	-0.004	(-0.02, 0.01)	0.64
Female sex	0.20	(-0.82, 1.21)	0.70
SF-36 Mental component score			
Intercept	52.52	(42.9, 62.1)	< 0.0001
FEV ₁ , % predicted	0.03	(-0.07, 0.14)	0.56
Age, yr	0.02	(-0.12, 0.15)	0.80
Whole lung emphysema proportion, -910 HU	2.76	(-2.64, 8.16)	0.32
Pack-years	-0.04	(-0.06, -0.01)	0.002
Female sex	-19.1	(-33.50, -4.74)	0.009
Age, yr · female sex	0.26	(0.04, 0.48)	0.02
QWB Score			
Intercept	0.394	(0.304, 0.483)	< 0.0001
FEV ₁ , % predicted	0.0008	(-0.0004, 0.002)	0.17
Age, yr	0.002	(0.0007, 0.003)	0.002
Whole lung emphysema proportion, -910 HU	0.056	(-0.005, 0.117)	0.07
Pack-years	-0.0004	(-0.0006, -0.001)	0.003
Female sex	-0.02	(-0.036, -0.003)	0.02
SGRQ Total Score			
Intercept	90.61	(81.31, 99.91)	< 0.0001
FEV ₁ , % predicted	-0.24	(-0.36, -0.11)	0.0002
Age, yr	-0.41	(-0.54, -0.28)	< 0.0001
Whole lung emphysema proportion, -910 HU	-7.69	(-14.09, -1.30)	0.02
Pack-years	0.03	(-0.0005, 0.05)	0.05
Female sex	0.02	(-1.68, 1.72)	0.98

Definition of abbreviations: HU = Hounsfield Unit; QWB = quality of well-being; SF-36 = Short form 36 health survey; UCSD SOBQ University of California, San Diego Shortness of Breath Questionnaire.

higher mBODE scores, higher depression scores, a lower SF-36 MCS, and a lower quality of well-being than men. Women also showed less severe overall emphysema than men, particularly in the lung peel, and smaller emphysema hole size, even with adjustment for FEV₁ % predicted, age, and smoking history. The small (< 2 mm diameter) airways of women had relatively thicker walls and disproportionately reduced airway lumens. By simultaneously correlating symptoms with carefully standardized physiological, radiological, and histological data, these results for the first time unite several previously separate lines of investigation in women's health and COPD.

These data showing greater breathlessness in women relative to men at similar degrees of airflow obstruction and emphysema severity are important because they imply that sex-specific anatomic differences must be considered in models of COPD pathogenesis. Interestingly, this difference was less evident after adjustment in IC/TLC, suggesting that part of this difference may relate to differences in lung volume. Our data agree with population-based studies in which women reported greater respiratory symptoms (3, 26-31), with two multinational studies based on physician-reported COPD, in which women were more likely to report severe dyspnea (2, 32), and with two case-control

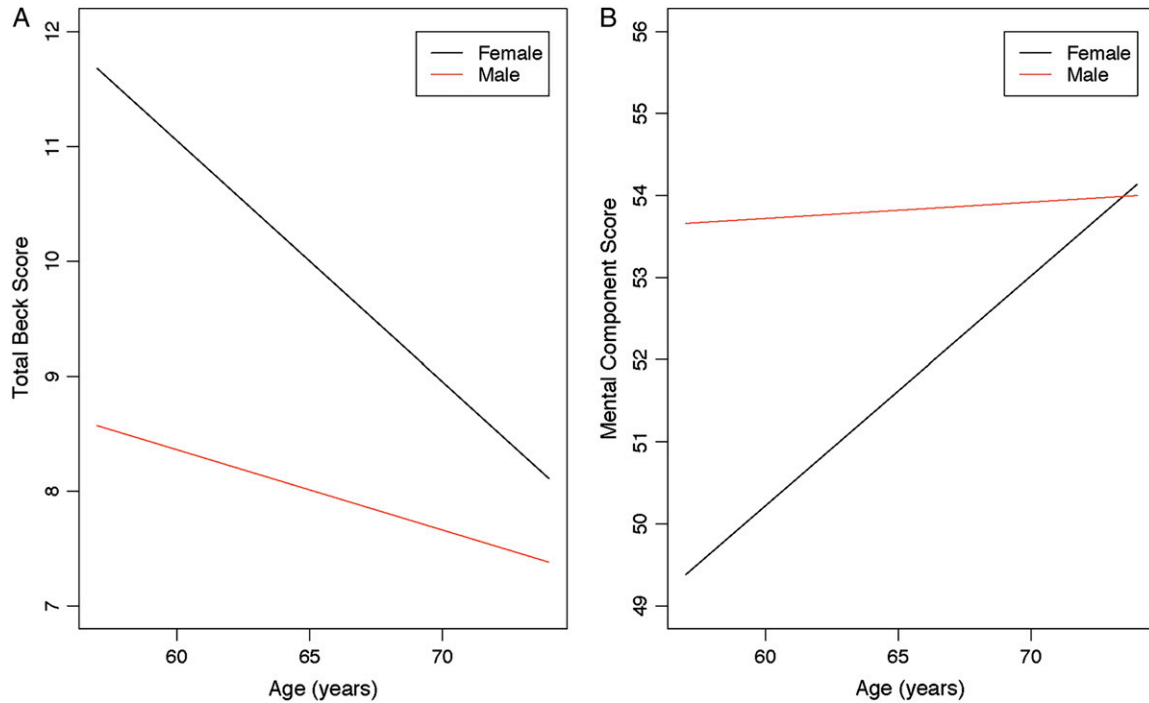


Figure 1. (A) Relationship of total Beck score (y axis) to age (x axis) when FEV₁% predicted, whole-lung % emphysema proportion, and pack-years are held constant. An interaction of age and sex is evident, and is significant ($P = 0.03$). (B) Relationship of SF-36 Mental Component Score (y axis) to age (x axis) when FEV₁% predicted, whole-lung % emphysema proportion, and pack-years are held constant. An interaction of age and sex is evident and is significant ($P = 0.02$).

studies (33, 34). The magnitude of difference in breathlessness in multivariate modeling in our data was above the level felt to be a minimal clinically important difference with this instrument (35). When the dyspnea score was incorporated in a validated

multidimensional index (36), the mBODE (17), we also found that women exhibited higher scores than men. Extending these findings using state-of-the-art quantitative CT imaging and histological techniques, our results lay the groundwork to integrate

TABLE 3. MULTIVARIATE MODELS PREDICTING EMPHYSEMA PROPORTION IN PATIENTS WITH SEVERE EMPHYSEMA ($N = 1,053$)

	Parameter Estimate	95% Confidence Interval	P Value
Whole-lung emphysema proportion (−950 HU)			
Intercept	0.270	(0.197, 0.341)	< 0.0001
FEV ₁ , % predicted	−0.0008	(−0.0018, 0.0003)	0.16
Age, yr	−0.001	(−0.0021, 0.00006)	0.06
Pack-years	−0.0003	(−0.0005, −0.00007)	0.01
Female sex	−0.164	(−0.305, −0.002)	0.02
Whole-lung emphysema proportion (−910 HU)			
Intercept	0.564	(0.483, 0.645)	< 0.0001
FEV ₁ , % predicted	−0.0025	(−0.004, −0.001)	< 0.0001
Age, yr	−0.0007	(−0.002, 0.0005)	0.28
Pack-years	−0.0004	(−0.0006, −0.0001)	0.004
Female sex	−0.030	(−0.046, −0.014)	0.0002
Whole-lung alpha (−950 HU)			
Intercept	0.87	(0.73, 1.01)	< 0.0001
FEV ₁ , % predicted	0.0001	(−0.002, 0.002)	0.96
Age, yr	0.002	(−0.0005, 0.004)	0.14
Pack-years	0.0005	(0.0001, 0.001)	0.02
Female sex	0.06	(0.03, 0.08)	< 0.0001
Whole-lung alpha (−910 HU)			
Intercept	0.60	(0.52, 0.69)	< 0.0001
FEV ₁ , % predicted	0.002	(0.0006, 0.003)	0.004
Age, yr	0.0006	(−0.0007, 0.002)	0.36
Pack-years	0.0003	(0.00007, 0.0006)	0.01
Female sex	0.02	(0.006, 0.04)	0.009

Definition of abbreviation: HU = Hounsfield Unit.

TABLE 4. HISTOLOGICAL FINDINGS IN MEN AND WOMEN WHO UNDERWENT VOLUME REDUCTION SURGERY IN THE NETT (N = 101)

	Males Mean (SD)	Females Mean (SD)	P Value
Number	59	42	
Age, yr	65.2 ± 6.4	66.3 ± 5.7	0.458
FEV ₁ , % predicted	24.5 ± 6.7	29.7 ± 7.0	0.001
Pack-years	71.7 ± 29.9	54.4 ± 19.8	0.003
Pi, mm*	2.63 (1.26)	2.37 (1.33)	0.026
Total wall area, mm ²	0.433 (0.301)	0.379 (0.327)	0.090
Total wall area/Pi*	0.256 (0.066)	0.267 (0.072)	0.040
Epithelium/Pi*	0.119 (0.026)	0.122 (0.031)	0.052
Muscle/Pi*	0.096 (0.029)	0.094 (0.029)	0.530
Lamina propria /Pi*	0.100 (0.034)	0.098 (0.031)	0.929
Adventitia/Pi*	0.175 (0.059)	0.190 (0.064)	0.004

* Expressed as square root of tissue area divided by the length of the basement membrane (Pi).

population-based COPD research with current concepts on the neuropsychological responses to stress and the molecular pathogenesis of inflammation.

Sex-specific Parenchymal and Airway Abnormalities in Relation to Airflow Limitation

The significant differences in the amount and distribution of emphysema in women compared with men are novel findings that encompass both severe (< -950 HU) and less severe (< -910 HU) emphysema. Few studies have examined the severity or distribution of emphysema in women with severe COPD. In a population-based study, patients with clinically defined emphysema were primarily male, whereas patients with chronic asthmatic bronchitis were predominantly female (37). Using state-of-the-art CT imaging, we confirm that emphysema is less severe in women, especially distally, and when present, is characterized by smaller hole size. Although the absolute differences between the sexes were modest, all analyses were remarkably consistent in their direction. Furthermore, in multivariate analysis adjusting for FEV₁, IC/TLC, mBODE, smoking history, and age, the proportion of severe emphysema was significantly lower in women, suggesting distinct differences in emphysema severity and distribution.

Whether comparable degrees of cigarette smoking induce greater reductions in lung function in female smokers is controversial, with data for (6, 26, 38–40) and against (41–43) that premise. Based on the ability to adjust for the proportion of emphysema, we noted a higher FEV₁% predicted in women at a given duration of cigarette smoking, and no significant interaction between sex and smoking history. Women in our cohort initiated smoking at a later age than men. Given their lower mean age at the time of randomization, these changes are consistent with those reported by other investigators (http://www.cdc.gov/tobacco/sgr/sgr_forwomen/pdfs/chp2.pdf), and may explain the lesser total pack-years of cigarette smoke exposure. Because our patients were selected for severe chronic airflow obstruction and an emphysematous phenotype, our data do not exclude the possibility that lung function deteriorates faster in female smokers during earlier stages of COPD (6, 26, 38–40, 44, 45). We noted a lower DL_{CO} in women despite lesser anatomic emphysema. This finding may relate to the complex contributions of lung mechanics and gas exchange which contribute to DL_{CO}. Interestingly, previous studies have identified a differential impact of central relative to distal emphysema on DL_{CO} (46). Thus, differences in emphysema distribution identified in women in the current study may help explain the differences in DL_{CO}.

The similarity between the sexes seen in FEV₁% predicted implies that women should have a greater degree of peripheral airway pathology (20). Indeed, using validated morphometric techniques to analyze airway histology in a subset of our patients with similar airflow obstruction and smoking history to the entire cohort, we confirm that women have smaller airway lumens and disproportionately thicker airway walls than men. This change would be anticipated to alter airway compliance and increase airways resistance. Theoretical analysis of the effect of airway wall thickness on resistance indicates that in proportion to the change in lumen radius even a minor thickening of the airway wall amplifies the effect of muscle shortening on lumen caliber and increases resistance of the airways (47).

Sex Differences in Health Status and Depression in Advanced COPD

Women in our study had worse health status, reflected in a lower QWB, although SF-36 PCS and SGRQ scores were similar in both sexes. These data are congruent with the limited data on sex differences in health status in COPD (48), which found that women expressed greater dissatisfaction with their lives (49), and were more likely to categorize their global self-reported health as “not very well” than as “well” (30). Recently, a small case control study suggested worse SGRQ in women (33), although this finding was not supported by others (34, 50). Women might report greater respiratory symptoms and worse health status because they perceive a given physiological perturbation differently (51).

Women in our study exhibited greater depression and significantly worse SF-36 MCS scores. In addition, age and sex interacted, with younger women exhibiting significantly greater Beck and lower SF-36 MCS scores than older women; this trend was much less evident in males. The magnitude of the difference in multivariate modeling is within the range identified for mild depression (15). Sex differences in depressive symptoms have recently been reported in COPD (34, 52). Furthermore, depression may potentiate the sensation of breathlessness (34, 53). Similar interactions between age and sex on depression have been reported previously in healthy subjects (54). Several explanations have been proposed for age and sex differences in depression, including differences in defensiveness and rumination, respectively (54). Older adults exhibit greater defensiveness (55) and an increased ability to regulate emotions (56). Importantly, women show greater defensiveness than men with increasing age. Rumination is associated with increased depression, is more common in women, and among women is inversely related to age (57). Younger women’s tendencies to feel less control over emotions and negative events, and feel a greater responsibility for the emotional tone of relationships, may mediate the relationship between rumination and depression (58). However, in another recent study (59) rumination and depression were positively associated with peripheral blood lymphocyte, leukocyte, and B cell counts, as well as health care utilization, in healthy older adults but not in younger adults. Our data cannot provide a mechanistic explanation for the reported differences, but suggest that additional investigation in this area is required.

Potential Sex-specific Differences in Smaller Airways and Parenchyma

Why cigarette smoking differentially affects the airways and lung parenchyma of men versus women is unclear. Potential explanations include greater baseline airway hyperresponsiveness in women (5, 60–62) and differences in particulate deposition within the airways (2, 4). The magnitude and character of the inflammatory response to cigarette smoke is likely to be

affected by sex hormones, for which several leukocyte subsets have receptors. Progesterone induces cyclical changes in IL-8 production (63) and promotes a Th2 cytokine response (64). Cyclical changes in estradiol concentrations in women have been associated with changes in lung adrenergic receptor density and in concentrations of mucus, acetylcholine, and prostaglandin (4). Estradiol also increases T cell expression of receptors for CC chemokines and alters T cell homing patterns (65). Interestingly, analysis of bronchoalveolar fluid in healthy individuals showed a significantly increased percentage of CD4+ T cells in women over age 43, compared with men and with younger women (66). Idiopathic cough, associated with lymphocytic inflammation manifest as bronchoalveolar lymphocytosis, is seen predominantly in older women (67). However, even though human innate and adaptive immune responses show complex degrees of sexual dimorphism that vary with the specific pathogen and over the life of the individual (68), current understandings of this dimorphism do not fully explain sex-based differences in COPD pathogenesis or phenotype, and most importantly, do not yet suggest opportunities for prevention or treatment.

Limitations of this study come from its highly selective sample population. All subjects were enrolled in NETT, a randomized trial of lung volume reduction surgery for patients with a predominantly emphysematous phenotype. As such, selection bias was imposed by requirements for sustained smoking cessation and absence of comorbidities or significant sputum production. Similarly, the requirement for severe emphysema limits generalizability to all patients with COPD, as does the potential of a referral bias varying by sex. On the other hand, no specific sex-related factors were included in the evaluation process or in the inclusion/exclusion criteria, which should minimize bias in the current analyses. The cross-sectional nature of the analyses also limits the ability to define mechanisms and distinct phenotypes. Nevertheless, the results of our study should be considered as hypothesis generating. It is possible that our findings on emphysema characteristics and airway abnormalities result principally from the greater size of the adult male lung. Importantly, sex differences in emphysema distribution and proportion persisted after extensive analyses adjusting for lung volume.

In summary, this study shows that women with severe COPD exhibit distinct disease manifestations than men. Relative to men, advanced COPD in women is characterized anatomically by smaller airway lumens and disproportionately thick airway walls, and by emphysema that is less extensive, manifest by smaller hole size and less peripheral involvement. These anatomic differences are accompanied by distinctive symptomatology. At a given FEV₁ predicted, age, and proportion of emphysema, female patients with COPD report greater breathlessness and depression, despite similar health status. Our data should motivate future studies to determine the complex interactions between biological and sociocultural factors (4) that contribute to these differences, and thus to provide a foundation for novel therapies to reduce the increasingly disproportionate burden of this common disease in women.

Conflict of Interest Statement: F.J.M. is a consultant for Altana Pharma and has received compensation greater than \$10K. He has been a member of several Advisory Boards, CME committees and the Speaker's Bureau for Boehringer Ingelheim (BI), Pfizer, and GlaxoSmithKline (GSK). Total compensation per company is greater than \$10K. In addition, he is on the advisory board for Novartis and speaker's bureau for Sepracor and Astra, receiving less than \$10K per company. He has been an investigator for industry-sponsored studies for GSK, BI, and Actelion. J.L.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.D.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.W. does not have a financial relationship with a commercial

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