Airway and Parenchymal Disease in Chronic Obstructive Pulmonary Disease Are Distinct Phenotypes

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The relative importance of genetic factors and tobacco smoking intensity in the pathogenesis of the airway disease and emphysematous components of chronic obstructive pulmonary disease (COPD) is unknown. We addressed this question in a family-based study that recruited probands ($FEV_1 < 60\%$ predicted, ages 45–65 yr, and > 5 pack-year smoking history) and their current/ex-smoking siblings. The family-based design allowed us to test the relationship between COPD phenotype (emphysema or small airway disease) in a proband and his or her siblings. Subjects completed a questionnaire and underwent spirometry, and a subset of participants underwent chest computed tomography (CT) scans.

Results: The number of pack-years was only weakly correlated with FEV_1 in 634 individuals with emphysema, as assessed by radiologist scoring of chest CT scans ($r = -0.09$, $p = 0.02$). The amount of emphysema on CT scan was inversely related to FEV_1 ($p < 0.001$), but there was no relationship between pack-years and amount of emphysema. Emphysema was more prevalent in the siblings of probands with emphysema (41.7%) than in siblings of nonemphysema probands (23.6%, $p < 0.001$); this was independent of pack-years smoked (adjusted odds ratio, 2.12; $p = 0.03$). In 482 individuals without emphysema, FEV_1 was correlated with pack-years smoked ($r = -0.38$, $p < 0.0001$). The correlation between pack-years and FEV_1 was particularly strong ($r = -0.58$, $p < 0.0001$) in 48 siblings who were from families in which the proband had predominantly small airway disease.

These data suggest that emphysema and airway-related COPD are distinct phenotypes and have different relationships with smoking. Moreover, differences in amount of emphysema are not explained by cumulative smoking, suggesting a complex gene–environment interaction.

Conflict of Interest Statement: B.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.M., on behalf of GlaxoSmithKline (GSK), over the last 3 years has served on advisory boards and received \$7,500. He spoke at GSK-sponsored programs and received \$18,000. He participated in multicenter clinical trials. His institution has received unrestricted educational grants from GSK and has received research grants for participating in GSK multicenter clinical trials. H.O.C. received \$11,000 in 2003 for serving on an advisory board for GSK. In addition, he is the coinvestigator on two multicenter studies sponsored by GSK and has received travel expenses to attend meetings related to the project. He has three contract service agreements with GSK to quantify the CT scans in subjects with COPD. A percentage of his salary between 2003 and 2006 (\$15,000/yr) derives from contract funds provided to a colleague, Peter D. Pare, by GSK for the development of validated methods to measure emphysema and airway disease using CT. There is no financial relationship between any industry and the current study. N.L.M. has a GSK-sponsored research grant on quantification of emphysema and airway abnormalities of CT

scans in patients with COPD. The value of the grant over the last 3 years has been approximately \$100,000/year. S.P. is a full-time employee of GSK. W.A. is a full-time employee of GSK and owns stock in GSK. E.S. received grant support, consulting fees, and honoraria from GSK for studies of COPD genetics. He also received a speaker's fee from Wyeth for a talk on COPD genetics. He has received honoraria from Bayer. D.L. has participated as a speaker in scientific meetings organized and financed by GSK. He received £5,000 as a consultant for GSK and £1,500 for serving on an advisory board for GSK. His research group has received £517,000 from GSK to fund the study reported in this paper and they will receive approximately £650,000 for the ECLIPSE study, which will assess the natural history of COPD, and to identify novel biomarkers for COPD (2006–2009).

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Relationship between Pathologic Characteristics of Peripheral Airways and Outcome after Lung Volume Reduction Surgery in Severe Chronic Obstructive Pulmonary Disease

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Background: Despite recent advances in the selection process for lung volume reduction surgery (LVRS), there remains significant variability in individual response. Our primary hypothesis was that variations in peripheral airway thickness and/or luminal mucous content contributed to variability in survival after LVRS. We further explored the relationship between these pathologic indices and changes in symptoms and physiology.

Methods: Participants included a total of 101 subjects undergoing LVRS as participants in the National Emphysema Treatment Trial (NETT; $n = 94$) and the University of Pittsburgh LVRS program ($n = 7$). Small (≤ 2 mm) airways were isolated from formalin-fixed and paraffin-processed lung specimens using digital-image analysis. Luminal content/maximal luminal area was represented as LC%. Survival was analyzed using uni- and multivariate proportional hazards models.

Results: Total airway wall thickness was not a predictor of survival. LC% as a continuous or categorical measure was a strong predictor of survival ($\geq 42\%$ [$n = 25$] vs. $< 42\%$ [$n = 74$]; hazard ratio [HR], 5.1; $p < 0.0001$; median survival, 3.2 vs. 6.6 yr), even after adjustments for age, sex, presence of upper lobe predominant emphysema and low exercise capacity and FEV_1 . Subjects with $LC\% \geq 42\%$ did not differ significantly from those with $LC\% < 42\%$ in baseline FEV_1 , RV or maximal

Figure 1. Percentage of luminal content (LC%) was a strong predictor of poor survival. Lowest quartile ($n = 25$) versus upper three quartiles ($n = 74$; hazard ratio [HR], 5.1; $p < 0.0001$).

exercise watts, cough, sputum, dyspnea, or quality of life (University of California, San Diego, Shortness of Breath; St. George Respiratory Questionnaire [UCSD-SOB; SGRQ]). At 24 months, ΔFEV_1 , ΔRV , and $\Delta SGRQ$ were similar. Subjects with $LC\% \geq 42$ had less improvement in watts and dyspnea at 24 months (Δ watts, -7.6 vs. $+5.5$; $p = 0.03$; Δ UCSD-SOB, $+1.9$ vs. -14.1 ; $p = 0.01$).

Conclusions: Increased peripheral airway LC% but not airway wall thickness is associated with poorer survival and a greater decline in exercise tolerance and dyspnea in subjects with chronic obstructive pulmonary disease after LVRS independent of established predictors. Notably, LC% was not associated with cough and sputum production. It is not clear whether the prognostic nature of airway luminal mucus is specific to patients undergoing LVRS or reflects the natural history of the disease.

Conflict of Interest Statement: F.C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.J.M. no longer has consulting or Speaker's Bureau activities with Intermune. His declaration covered activities dating to the last calendar year. He is a coinvestigator in the GIPF-007 study. His total compensation with this company has been less than \$10,000. His interaction with Actelion has been as principal investigator of the BUILD 1 at the University of Michigan. His personal total compensation is less than \$10,000. He has no leadership role in activities for this company. Encysive:

He has been a member of the steering committee for a selective endothelin antagonist being investigated in scleroderma-related pulmonary parenchymal disease. Given the potential conflict with IPF NET studies, he has relinquished his role on this steering committee. Co-Therix: He has been a member of the steering committee for an inhaled vasodilator (Iloprost) in IPF-related pulmonary hypertension. This relationship has ended. He has been a member of several advisory boards, CME committees, and the Speaker's Bureau for Pfizer relating exclusively to COPD. His total compensation is greater than \$10,000, but less than \$20,000. He has been a member of several advisory boards, CME committees, and the Speaker's Bureau for Boehringer Ingelheim relating exclusively to COPD. His total compensation is greater than \$10,000, but less than \$20,000. He has not been involved with any IPF-related compounds. R.M.R. received lecture fees from Boehringer Ingelheim for six to eight talks at various locations (\$10,000). B.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.M.C. is Chairman at Glaxo Data Safety Monitoring Board (DSMB). S.A.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.O.C. received \$11,000 in 2003 for serving on an advisory board for GlaxoSmithKline (GSK). In addition, he is the coinvestigator on two multicenter studies sponsored by GSK and has received travel expenses to attend meetings related to the project. He has three contract service agreements with GSK to quantify the CT scans in subjects with COPD. A percentage of his salary between 2003 and 2006 (\$15,000/yr) derives from contract funds provided to a colleague, Peter D. Pare, by GSK for the development of validated methods to measure emphysema and airway disease using CT. There is no financial relationship between my industry and the current study. A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.D.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.C.H. has been paid for giving lectures at national and international meetings by Altana, GSK, and AstraZeneca (AZ), and has received approximately \$10,000 for this activity. He has also served as a consultant for Altana, GSK, and AZ, and has received approximately \$15,000 for this activity. He currently serves as a principal investigator on a 2-year Canadian Institutes of Health Industry-sponsored grant on COPD that was awarded to the University of British Columbia.

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