The Relationship Between Pulmonary Emphysema and Kidney Function in Smokers

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Background: It has been reported that the prevalence of kidney dysfunction may be increased in patients exposed to tobacco with airflow obstruction. We hypothesized that kidney dysfunction would associate with emphysema rather than with airflow obstruction measured by the FEV₁.

Methods: Five hundred eight current and former smokers completed a chest CT scan, pulmonary function tests, medical questionnaires, and measurement of serum creatinine. Glomerular filtration rates (eGFRs) were estimated using the method of the Chronic Kidney Disease Epidemiology Collaboration. Quantitative determinants of emphysema and airway dimension were measured from multidetector chest CT scans.

Results: The mean age was 66 ± 7 years, and mean eGFR was 101 ± 22 mL/min/1.73 m². Univariate and multivariate analysis showed a significant association between radiographically measured emphysema and eGFR: Participants with 10% more emphysema had an eGFR that was lower by 4.4 mL/min/1.73 m² ($P = .01$), independent of airflow obstruction (FEV₁), age, sex, race, height, BMI, diabetes mellitus, hypertension, coronary artery disease, patient-reported dyspnea, pack-years of smoking, and current smoking. There was no association between eGFR and either FEV₁ or quantitative CT scan measures of airway dimension.

Conclusions: More severe emphysema, rather than airflow obstruction, is associated with kidney dysfunction in tobacco smokers, independent of common risk factors for kidney disease. This finding adds to recent observations of associations between emphysema and comorbidities of COPD, including osteoporosis and lung cancer, which are independent of the traditional measure of reduced FEV₁. The mechanisms and clinical implications of kidney dysfunction in patients with emphysema need further investigation.

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Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DM = diabetes mellitus; DXA = dual x-ray absorptiometry; eGFR = estimated glomerular filtration rate; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAA = low attenuation area; NT-proBNP = N-terminal pro-brain natriuretic peptide; SCCOR = Specialized Center for Clinically Oriented Research

COPD is a heterogeneous disease associated with multiple comorbidities, including lung cancer, cardiovascular disease, and osteoporosis.^{1–4} These comorbidities are estimated to produce as much morbidity and mortality in patients with COPD as the lung disease per se.⁵ It is increasingly evident that some comorbidities of COPD are preferentially associated with different COPD phenotypes. For example, osteoporosis and lung cancer have been preferentially associated with the emphysema phenotype rather than the airflow obstruction phenotype (reduction in FEV₁).^{6,7}

It has been reported that the prevalence of kidney dysfunction is increased in those with COPD.^{8,9} We hypothesized that, similar to osteoporosis and lung cancer, kidney dysfunction is preferentially associated with the emphysema phenotype of COPD rather than with airway obstruction and that this association is independent of common risk factors for kidney failure, such as advanced age, diabetes mellitus (DM), and hypertension.

Studying the association between emphysema and kidney function is important because emphysema is highly prevalent and there is significant morbidity,

mortality, and cost associated with kidney failure and kidney replacement therapy. Furthermore, such an association may provide insight into the complex relationships between the pulmonary phenotypes and systemic manifestation of COPD.

MATERIALS AND METHODS

We used data from 508 current and former smokers enrolled in the Specialized Center for Clinically Oriented Research (SCCOR) study at the University of Pittsburgh to investigate our hypothesis. SCCOR participants were primarily recruited from those previously enrolled in the Pittsburgh Lung Screening Study cohort. They were 40 to 79 years old with a minimum 10 pack-year smoking history. Subjects were excluded if they had a restrictive pattern on spirometry, other significant lung disease, uncontrolled comorbidity including a cardiovascular event or congestive heart failure exacerbation in the preceding year, prior thoracic surgery, or a BMI > 35 kg/m².

Each subject completed demographic and medical history questionnaires, had a chest multidetector CT scan, prebronchodilator and postbronchodilator spirometry, plethysmography, and blood sample collection. The study protocol was approved by the University of Pittsburgh Institutional Review Board (approval number IRB0612016), and written informed consent was obtained from each participant.

Estimation of Glomerular Filtration Rates

Creatinine levels were measured by a standard Jaffe method using a kit specific for plasma calibrated to the National Institute of Standards and Technology creatinine standard (Enzo Life Sciences, Inc), which had been collected at the time of enrollment and stored at -80°C. The serum creatinine was used to estimate the glomerular filtration rate (eGFR) using the equation described by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).¹⁰

CT Scan Examination and Pulmonary Function Testing

Chest CT scan examinations were performed with a LightSpeed VCT 64-detector scanner (General Electric Company) with

100 mAs of radiation exposure without IV contrast, as describe previously.¹ Emphysema severity was assessed by both density mask analysis and visual interpretation. Density mask analysis was used to quantify pixels associated with emphysema (or low attenuation area [LAA%]) using a -950 Hounsfield unit threshold and is reported as the percentage of the number of total voxels identified as lung regions (LAA%).¹¹ Visual interpretation was performed by a chest radiologist blinded to subject identities who scored the severity of visual emphysema using a 6-point scale: no emphysema = 0, <10% emphysema = 1 point, 10% to 25% emphysema = 2 points, 26% to 50% emphysema = 3 points, 51% to 75% emphysema = 4 points, and >75% emphysema = 5 points. There was a strong correlation between density mask and visual assessment of emphysema ($r = 0.74$, $P < .001$).

Airway analysis was performed using multiple airway sections depicted in axial CT images that were automatically detected.¹² Morphometry of the airways sections was computed using an algorithm that assigned pixels complete or partial membership to the airway lumen or wall. The algorithm was developed to capture partial volume averaging inherent in CT images.¹² Airway parameters were computed as the mean across all airway sections that were not at or near a bifurcation. Wall area percent and lumen perimeter were computed using methods described previously for all detected airway sections and for airway sections that represented the lowest tertile based on size (small airways).¹³

Pulmonary function testing was performed per the recommendations of the American Thoracic Society and measured values were compared with standard population-derived predicted values.^{14,15} Postbronchodilator spirometric values were used for all analyses.

Data on Covariates

N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured by a commercially available electrochemiluminescence-based immunoassay (Roche Elecsys 2010 analyzer; Roche Diagnostics) according to the manufacturer's instruction. The diagnosis of coronary artery disease was established on the basis of self-reported history of angina, myocardial infarction, or coronary revascularization. Diagnosis of hypertension was established on the basis of prescription for any BP-lowering medication, whereas DM was diagnosed on the basis of prescription for DM medications or patient report, so that both diet-controlled or medically treated DM were identified. Fat-free mass was assessed using whole-body dual x-ray absorptiometry (DXA) measurements of body composition, which were available for 271 participants.

Statistical Analysis

Univariate linear regression analyses were initially performed with patient characteristics and test results as predictors of eGFR. Results are reported as β coefficients (slope of the regression line) with their SEs and P values. For ease of interpretation, univariate data are also presented across tertiles of eGFR. Next, a bivariate linear regression model was created with LAA% and FEV₁ as predictors of eGFR to allow head-to-head comparison between the two variables. Finally, a multivariate linear regression model was created that also included age, race, height, BMI, hypertension, DM, coronary artery disease, and any variable associated with eGFR with $P < .2$ on univariate analysis.

We performed a number of secondary analyses to examine the robustness of our methodology and results. All equations that estimate GFR make assumptions about body composition.¹⁰ Because worsening emphysema is associated with loss of muscle mass, these equations can overestimate GFR in patients with severe emphysema. Therefore, we added fat-free mass to our multivariate model even if it was nonsignificant on univariate analysis. Also, analyses were repeated with creatinine as the outcome instead of eGFR. Finally, we used tertiles of eGFR as the outcome, instead

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of continuous eGFR, to ensure that outliers with spuriously high or low eGFR were not responsible for any significant association.

Increasing severity of emphysema is associated with increase in pulmonary vascular resistance and decreased cardiac output,¹⁶ which can reduce kidney perfusion and eGFR. Therefore, we performed a secondary analysis in which we added NT-proBNP, a validated biomarker of right and left ventricular volume overload,^{17,18} to our multivariate model. Also, because NT-proBNP can sometimes be falsely elevated (> 100 pg/mL) in patients with reduced renal function, we repeated the analysis excluding patients with NT-proBNP > 100 pg/mL.

To extend our results to the visual emphysema score, we repeated the analysis using the visual score in place of LAA% as a predictor of eGFR. Because a number of participants had normal spirometry, we repeated our analysis in patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage I to IV airflow obstruction.

Analyses were performed using STATA version 10.0 (StataCorp). Summary statistics are reported as means $\pm$ SD for continuous variables and proportions (%) for categorical variables. Statistical significance was defined as two-tailed $P < .05$.

RESULTS

Mean age of the 508 participants was 66 ± 7 years, and 55% were men (Table 1). Most participants had mild expiratory airflow obstruction and mild emphysema (Fig 1). Likewise, the kidney function of most participants was normal or mildly reduced (Fig 1).

Among the significant univariate predictors of eGFR was LAA% (% emphysema): Each 10% increase in LAA% was associated with a 3.7 mL/min/1.73 m² decline in eGFR ($P = .02$) (Figs 2, 3, Table 1). In contrast, FEV₁, wall area %, and the lumen perimeter of all airways and small airways were not significant univariate predictors (Fig 2, Table 1). BMI and lean body mass did not vary across tertiles of eGFR. Although NT-proBNP levels were significantly higher in those with low eGFR, it must be kept in mind that NT-proBNP levels are affected by kidney function and can be spuriously high (ie, > 100 pg/mL in those with low eGFR).

On bivariate linear regression, the addition of FEV₁ to the univariate model that included LAA% and eGFR led to a strengthening of the association. For each 10% increase in low attenuation units there was a 4.6 mL/min/1.73 m² decline in eGFR ($P = .009$).

In the multivariate linear regression model, each 10% increase in LAA% was associated with a 4.4 mL/min/1.73 m² decline in GFR ($P = .01$) independent of FEV₁, age, sex, race, height, BMI, DM, hypertension, coronary artery disease, patient-reported dyspnea, pack-years of smoking, and current smoking (Table 2). Although significant on univariate analysis, the diffusion capacity of lung for carbon monoxide was not included in the multivariate model because of significant collinearity with LAA% ($r = -0.6$, $P < .001$).

Replacing creatinine as the outcome in place of eGFR, using tertiles of eGFR as the outcome, exclusion

of patients with NT-proBNP > 100 pg/mL, or inclusion of NT-proBNP in the model in Table 2 did not substantially affect the results. Addition of DXA-derived fat-free mass did not affect the β coefficient for emphysema ($\beta = -0.46$); however, there was significant collinearity leading to a threefold increase in the SE and an accompanying increase in P value ($P = .133$). Also, the sample size decreased from 508 to 271 because only a fraction of the cohort had undergone DXA scans. Restricting the analysis to patients with GOLD stage I to IV airflow obstruction ($n = 273$) did not affect the association between emphysema and kidney function ($\beta = -0.47$, $P = .004$).

The visual emphysema score was also a significant predictor of eGFR: For each point increase in visual emphysema, the eGFR decreased by 2.6 mL/min/1.73 m² ($P = .001$) independent of the covariates listed in Table 2. Also, log transformation of LAA%, which was not normally distributed in our cohort, did not affect the independent association between emphysema and kidney function ($P = .01$).

DISCUSSION

We found a clinically and statistically significant reduction in kidney function with worsening emphysema independent of expiratory airflow obstruction (FEV₁) and common risk factors for kidney disease in a cohort of current and former smokers. To our knowledge, no prior study has investigated the association between emphysema and kidney function. However, two studies have reported increased prevalence of kidney dysfunction in those with spirometrically defined COPD. The first study included 3,358 patients undergoing vascular surgery and reported that COPD GOLD stage II was associated with kidney insufficiency, but not GOLD I or III.⁸ The COPD diagnosis was determined solely by clinical symptoms in 18% of their cohort. The second study included 356 patients and reported that the presence of COPD was associated with overt kidney failure (eGFR < 60 mL/min/1.73 m²) with an OR of 1.94 (95% CI, 1.01-4.66) independent of age, BMI, and diabetes.⁹ In both studies, there was no association between the severity of airflow obstruction and kidney function, similar to our analysis. In fact, in our analysis emphysema was dominant over FEV₁ in predicting kidney function (Table 2).

The classification of COPD based simply on magnitude of forced expiratory flow abnormality is inadequate and of limited value in individualizing therapeutic interventions to influence the natural history of the disease.² Despite a common etiologic agent, tobacco smoke, the individual variation in disease expression is remarkable. Airflow limitation is caused by a combination of the loss of lung elastic recoil and primary airway pathology; however, individuals with

Table 1—Univariate eGFR and Patient Characteristics and Test Results in a Cohort of 508 Participants Exposed to Tobacco

Variable	All (Mean ± SD)	Tertiles of Kidney Function			Univariate Linear Regression (Outcome eGFR)		
		High	Intermediate	Low	β	SE	P Value
eGFR, mL/min/1.73 m ²	101 ± 22	125 ± 17	101 ± 4	80 ± 13	...	...	...
Percent emphysema (LAA%)	3.4 ± 6.4	2.7 ± 5.4	3.1 ± 5.5	4.4 ± 8.0	−0.37	0.15	.02
FEV ₁ , % predicted	82 ± 21	82 ± 20	82 ± 21	82 ± 22	0.01	0.05	.76
Wall area %							
All airways ^a	47.7 ± 4.9	48.2 ± 5.1	47.5 ± 4.8	47.6 ± 4.8	0.22	0.20	.28
Small airways	49.0 ± 4.8	49.4 ± 5.0	48.9 ± 4.8	48.8 ± 4.6	0.25	0.20	.21
Lumen perimeter, mm ²							
All airways	17.9 ± 1.4	18.0 ± 1.4	17.9 ± 1.5	17.9 ± 1.3	0.58	0.69	.40
Small airways	14.8 ± 1.1	14.9 ± 1.2	14.8 ± 1.2	14.8 ± 1.1	0.54	0.85	.53
Age, y	66 ± 7	63 ± 5	66 ± 6	69 ± 6	−1.30	0.14	<.001
Sex, % male	55	59	51	50	4.20	1.96	.03
Race							
White	94.5	92.5	97.6	93.2	Reference		
Black	4.5	6.8	1.7	5.1	−1.3	4.7	.79
Other	1.0	0.6	0.6	1.7	−1.1	9.9	.92
Height, cm	169.3 ± 9.4	170.0 ± 9.1	168.9 ± 10.1	169.1 ± 9.1	0.15	0.11	.15
BMI, kg/m ²	28 ± 4	28 ± 4	28 ± 4	28 ± 4	0.02	0.20	.90
Lean mass (n = 271), kg	53 ± 12	52 ± 11	53 ± 12	53 ± 12	0.14	0.12	.21
Smoking, pack-y	57 ± 33	51 ± 30	57 ± 28	61 ± 39	−0.08	0.03	.007
Current smoking, yes, %	44.9	52.8	43.9	38.6	2.8	1.97	.15
Diabetes mellitus, %	9	7	11	12	−3.90	3.38	.25
Hypertension, %	40	33	38	46	−4.80	1.99	.02
Systolic BP, mm Hg	132 ± 16	131 ± 15	132 ± 16	134 ± 17	−0.13	0.06	.03
Oxygen saturation, %	96.5 ± 1.76	96.6 ± 1.7	96.6 ± 1.7	96.5 ± 1.8	−0.17	0.57	.76
Coronary artery disease, %	14	10	18	18	−2.50	2.79	.38
MMRC Dyspnea	1.59 ± 1.20	1.46 ± 1.20	1.53 ± 1.21	1.77 ± 1.18	−2.20	0.81	.008
Questionnaire score							
DLCO, % predicted	71 ± 19	75 ± 19	72 ± 18	67 ± 18	0.22	0.05	<.001
NT-proBNP, pg/mL	106 ± 277	67 ± 90	77 ± 103	169 ± 445	−0.01	0.003	<.001

P values from univariate regression analysis are reported in the last column. DLCO = diffusing capacity of lung for carbon monoxide; eGFR = estimated glomerular filtration rate; LAA% = percentage of low attenuation area associated with emphysema based on the density mass analysis of CT scans; MMRC = Modified Medical Research Council; NT-proBNP = N-terminal pro-natriuretic peptide.

^aWall area as a percentage of total airway area.

^bMean airway perimeter of all airways.

identical FEV₁ can vary dramatically with respect to the extent and distribution of parenchymal emphysema or airway inflammation and remodeling. Furthermore, there is a poor relationship between FEV₁ and global measures that assess symptoms or functional impairments and the presence of comorbidities. The cellular and molecular events that lead to these variations in disease progression and the relative influence of genetic and environmental factors remain poorly understood.^{2,19} Our findings warrant further investigation into the shared molecular and cellular mechanistic links between the pulmonary emphysema phenotype of COPD and its comorbidities.

The existence of an emphysema-kidney injury phenotype, as suggested by our results, may have important clinical implications. In patients with emphysema, kidney dysfunction may be contributing to the development of systemic manifestations, including osteoporosis,¹ cardiovascular disease,⁵ and anemia,²⁰ whereas

in patients with chronic kidney disease unsuspected and therefore undiagnosed emphysema may be contributing to the significant limitation in exercise capacity and quality of life frequently present in these patients.²¹ Although our study lacked longitudinal follow-up to estimate the cumulative effect of emphysema on renal function, and participants with known renal disease were excluded, our data suggest that the effect of emphysema on renal function is modest and insufficient to produce overt renal failure in the absence of other risk factors.

The mechanisms that link emphysema and kidney function are at present speculative. Emphysema can produce right ventricular volume overload by increasing pulmonary vascular resistance¹⁶ leading to reduced cardiac output and kidney perfusion with resulting reductions in eGFR. To explore the influence of this mechanism, we excluded patients with even mild elevations in NT-proBNP and found no effect on the

FIGURE 1. A-C, The distribution of GOLD stage (A), severity of emphysema on visual examination of chest CT scans (B), and estimated glomerular filtration rate (C) in 508 participants exposed to tobacco in the Specialized Center for Clinically Oriented Research study. GOLD = Global Initiative for Chronic Obstructive Lung Disease.

association. This argues against increased pulmonary vascular resistance as the principal mechanism. Another explanation could be a cellular or immune complex mediated systemic inflammatory response in patients with emphysema,²² similar to other chronic inflammatory conditions such as rheumatoid arthritis²³ and chronic hepatitis C infection.²⁴ Such an inflam-

matory response can lead to kidney dysfunction either directly or by induction of endothelial dysfunction, which has been associated with kidney dysfunction previously.²⁵

The lack of an association between known risk factors such as history of diabetes, hypertension, and vascular disease with reduced kidney function in our

FIGURE 2. A, B, Fitted regression lines with 95% CIs depicting the association between low attenuation area % (LAA%) (percent emphysema) and estimated glomerular filtration rate (eGFR) (A), and % predicted FEV₁ and eGFR (B). Percent emphysema is presented on the log base 10 scale to aid visual interpretation.

FIGURE 3. Fitted regression line depicting the association between LAA % (percent emphysema) on the linear scale and eGFR. See Figure 2 legend for expansion of abbreviations.

analysis deserves comment. In univariate analysis, those with reduced kidney function had more diabetes, more vascular disease, and higher BPs (Table 1), although the *P* value was only significant for BP. We believe that the reason for the statistical nonsignificance is not a lack of underlying association but rather the lack of statistical power to detect these associations due to the low prevalence of diabetes (9%) and vascular disease (14%) relative to history of hypertension (40%) and emphysema (62%) (Fig 1). The low prevalence of diabetes and vascular disease is not surprising, because our cohort mostly included relatively healthy community-based smokers. Also, those who did have high BP had mild BP elevation (median systolic BP, 143 mm Hg; interquartile range, 130-150 mm Hg). The univariate association between hypertension and reduced kidney function was not attenuated by

Table 2—Multivariate Linear Regression Model With eGFR as the Outcome Variable

Variable	β	SE	<i>P</i> Value
Percent emphysema (LAA%)	−0.44	0.17	.01
FEV ₁ , % predicted	−0.08	0.05	.11
Age, y	−1.25	0.14	<.001
Sex, male	7.90	2.64	.003
Race			
White	Reference	...	...
Black	−0.99	4.44	.82
Other	−5.80	9.18	.53
Height, cm	−0.46	0.34	.18
BMI	−0.13	0.26	.61
Hypertension, mm Hg	−2.42	1.91	.22
Diabetes mellitus	−1.31	3.27	.69
Coronary artery disease	−0.94	2.68	.73
MMRC Dyspnea Questionnaire score	−0.62	0.88	.48
Smoking, pack-y	−0.04	0.03	.16
Current smoking, yes	−0.44	1.89	.86

See Table 1 legend for expansion of abbreviations.

adjusting for emphysema. It should also be noted that diffusion capacity and emphysema were both independently associated with reduced kidney function in our analysis and were collinear with each other. Therefore, the relationship between emphysema and reduced kidney function can also be thought of as a relationship between low diffusion capacity and reduced kidney function.

Certain limitations of our study must be considered when interpreting the results. GFR was estimated and not directly measured using clearance studies because these were not feasible in our outpatient cohort. Even though the CKD-EPI equation has been shown to perform better in patients with normal or near-normal GFR, with less bias, improved precision, and greater accuracy than the Modification of Diet in Renal Disease (MDRD) equation used by the two previous studies linking COPD and renal function,¹⁰ all estimation equations have limitations. These limitations arise because the equations rely on the serum creatinine, which can be affected by fat-free mass and muscle turnover, in addition to GFR. Accordingly, we performed multiple secondary analyses, including one in which we used serum creatinine as the outcome in place of eGFR, and another in which we included DXA-derived fat-free mass in the multivariate model, which did not indicate presence of significant bias due to the use of eGFR. A large majority of our cohort had normal or mildly decreased kidney function. Therefore, even though the relationship between increasing emphysema and kidney function appeared linear, longitudinal investigation of patients with more severe emphysema or advanced kidney dysfunction is warranted. Because age and sex are known to affect kidney function, their statistical significance in our multivariate model is not surprising. However, the magnitude of the effects for these two variables should be interpreted with caution, because age and sex are included in the CKD-EPI equation and therefore may appear to be more strongly associated than otherwise. Data on smoking, diabetes, and hypertension were self-reported and are therefore subject to misclassification. Similarly, the precision of our assessment of tobacco exposure would have been enhanced if a biologic measure of tobacco exposure, such as urine cotinine level, had been measured. Finally, our study lacked data on microalbuminuria, which may be a biomarker of early kidney injury in patients with emphysema.²⁶

In summary, the present data identify a significant reduction in kidney function with increasing severity of emphysema, independent of expiratory airflow obstruction and common risk factors for kidney injury. The pathophysiology of this association, and its clinical implications, warrant further investigation given the potential mechanistic insights that might be

gained into the phenotypes of COPD and its systemic manifestations.

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Dr Chandra: contributed to study conception and design, analysis and interpretation, and drafting the manuscript for important intellectual content.

Dr Stamm: contributed to study conception and design, analysis and interpretation of data, and drafting the manuscript for important intellectual content.

Dr Palevsky: contributed to analysis and interpretation of data and drafting the manuscript for important intellectual content.

Dr Leader: contributed to drafting the manuscript for important intellectual content.

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Dr Branch: contributed to drafting the manuscript for important intellectual content.

Dr Weissfeld: contributed to drafting the manuscript for important intellectual content.

Dr Gur: contributed to analysis and interpretation of data and revision of the manuscript.

Dr Gladwin: contributed to study conception and design and drafting the manuscript for important intellectual content.

Dr Sciruba: contributed to study conception and design, analysis and interpretation of data, and drafting the manuscript for important intellectual content.

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