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ORIGINAL RESEARCH

Computed Tomographic-Based Quantification of Emphysema and Correlation to Pulmonary Function and Mechanics

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ABSTRACT

Computed tomographic based indices of emphysematous lung destruction may highlight differences in disease pathogenesis and further enable the classification of subjects with Chronic Obstructive Pulmonary Disease. While there are multiple techniques that can be utilized for such radiographic analysis, there is very little published information comparing the performance of these methods in a clinical case series. Our objective was to examine several quantitative and semi-quantitative methods for the assessment of the burden of emphysema apparent on computed tomographic scans and compare their ability to predict lung mechanics and function. Automated densitometric analysis was performed on 1094 computed tomographic scans collected upon enrollment into the National Emphysema Treatment Trial. Trained radiologists performed an additional visual grading of emphysema on high resolution CT scans. Full pulmonary function test results were available for correlation, with a subset of subjects having additional measurements of lung static recoil. There was a wide range of emphysematous lung destruction apparent on the CT scans and univariate correlations to measures of lung function were of modest strength. No single method of CT scan analysis clearly outperformed the rest of the group. Quantification of the burden of emphysematous lung destruction apparent on CT scan is a weak predictor of lung function and mechanics in severe COPD with no uniformly superior method found to perform this analysis. The CT based quantification of emphysema may augment pulmonary function testing in the characterization of COPD by providing complementary phenotypic information.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by incompletely reversible airflow obstruction due to small airways remodeling and dynamic expiratory airways collapse secondary to the presence of emphysema. Classically, subjects with COPD were thought to have a preponderance of either emphysema or airways disease (1); however, these processes are no longer thought of as mutually exclusive but rather coincident and likely additive with regard to functional impairment (2). While current standards for the diagnosis and staging of COPD are based largely upon spirometric measures of lung function (3), such metrics are insensitive to the etiology of functional impairment. Because of this, new methods are being sought to augment the characterization of subjects with COPD (4). One such tool is analysis of Computed Tomographic (CT) imaging of the lungs.

There are several CT based methods commonly employed in clinical investigation for the assessment of the burden of emphysema, including such techniques as a semi-quantitative visual scoring systems and more automated densitometric analyses (5–11). Prior investigations have reported correlations of such metrics of emphysema and measures of lung function (12–15). The literature also suggests that CT imaging may aid in the selection of subjects for therapeutic interventions such as surgical lung volume reduction (16, 17).

Questions remain, however, regarding the selection of an optimal method for CT scan analysis and the impact of using these different techniques on correlative studies to lung function and mechanics. Data from a large cohort of well-characterized subjects enrolled in the National Emphysema Treatment Trial (NETT) will allow examination of the performance and comparability of these methods. Such an examination may also provide insight into the remarkable heterogeneity of the pulmonary processes present in COPD. Aspects of this analysis have been published in abstract form (18).

METHODS

During active patient enrollment in the NETT, 1218 patients underwent functional and radiographic testing after rehabilitation and prior to randomization (16). Of these, 1094 of these patients had CT scans and corresponding pre-randomization pulmonary function tests that were used in this investigation. Post-randomization data was excluded from this analysis. Subjects were included in the NETT if they had CT scan evidence of bilateral emphysema, a post-bronchodilator TLC and RV of $\geq 100\%$ and 150% respectively and a post-bronchodilator FEV_1 of $\leq 45\%$ predicted. Detailed inclusion and exclusion criteria for study enrollment can be found Supplementary Appendix 1 of the primary outcomes publication (http://www.nejm.org) (16).

CT scans

Imaging protocols were established for single slice spiral CT scanners (General Electric, Siemens, and Picker). Using an equivalent standard or "lung" reconstruction algorithm for each brand of scanner, volumetric imaging data was collected without intravenous contrast using a collimation of 5–8 mm, pitch of 1.7:1, 50% overlap, a field of view (FOV) defined by the outer ribs at their widest dimension, and 120 to 140 kVp. Study subjects were instructed to perform 3 to 4 hyperventilatory breaths immediately prior to imaging. The CT scans were then acquired in a cranial to caudal direction with the subject holding their breath at full inflation (TLC).

Computed tomographic based measures of emphysema were performed using Hounsfield Unit thresholds of −950, −930, −910, −850, and −810 and a software package developed by the University of Iowa (Pulmonary Analysis Software Suite). These measures were calculated for both the whole and regional lung fields. In the latter case, the lung was divided into equal upper, middle, and lower thirds based upon cranial-caudal height. Additional densitometric measures used for this investigation include the mean lung density (HU) and the HU threshold below which 15% of the lung voxels fall (Perc15) (19).

A second set of high-resolution CT scan images was obtained contemporaneously with the conventional scans. Radiologists visually scored these image sets using a 5-point ordinal system applied to each of 3 regions in each lung defined as the lung apex to the top of the aortic arch (upper zone), aortic arch to the right inferior pulmonary vein (mid zone), and the right inferior pulmonary vein to the most caudal extent of the lungs (lower zone) (16). "Zero" was defined as normal or having no emphysema, 1 as mild or 1–25% emphysema, 2 as moderate with 26–50% emphysema, 3, marked with 51–75% emphysema and 4 as severe with >75% emphysema. This was performed on the left and right lung with a total possible score of 24 if all 6 regions consisted of >75% emphysema. The sum of these regional scores for each subject was used for correlation studies.

Pulmonary function tests

Pulmonary function test data included spirometry, lung volumes, and diffusing capacity for carbon monoxide. Each of the 17 clinics participating in the trial used their own pulmonary function lab following American Thoracic Society guidelines (20, 21). Post-bronchodilator values of lung function were used for this analysis.

Lung mechanics

At the time of subject randomization, a subset of 225 subjects underwent placement of an esophageal balloon catheter to estimate pleural pressure (22). Static transpulmonary pressures at total lung capacity were reported as static lung recoil.

Statistical analysis

Univariate measures of pulmonary function, the percent of emphysema on the CT scans, the sum of the radiologist scores, and the measures of lung mechanics were treated as continuous data. Pearson correlation coefficients for each of the Hounsfield Unit thresholds and measures of pulmonary function were assessed. p values <.001 (Bonferroni adjusted $\acute{\alpha} = 0.05/50 =$

Table 1. Characteristics of subjects including post rehabilitation, post bronchodilator pulmonary function measurements and corresponding pre rehabilitation CT scans (n = 1094 unless specified)

Subject Characteristic	Mean (SD)
Female	427 (39%)
Male	667 (61%)
Age (years)	67.0 (+/− 6.2)
FEV_1 % predicted	26.9 (+/− 7.2)
FVC % predicted	67.7 (+/− 15.4)
FEV_1/FVC	0.31 (+/−.06)
TLC % predicted	128.2 (+/− 15.0)
RV % predicted	221.0 (+/− 49.3)
RV/TLC	0.64 (+/− 0.08)
DLCO % predicted*	28.5 (+/− 9.7)
% Emphysema (−910 HU)	42.5 (+/− 12.3)
Radiologist Score	16.5 (+/− 3.8)

FEV_1: Forced expiratory volume in 1 second.
FVC: Forced vital capacity.
TLC: Total lung capacity.
RV: Residual volume.
DLCO: Diffusing capacity for carbon monoxide.
n = 1085.

0.001) were considered to be statistically significant. SAS Version 8.2 (Cary, NC) was used for statistical analysis.

RESULTS

Patient characteristics at time of enrollment are provided in Table 1. A total of 1094 CT scans with corresponding pulmonary function tests were available for analysis in all categories except for the percent-predicted DLCO. Figure 1 illustrates the effect of HU threshold selection on the percent emphysema in the cohort. As shown, the percentage of lung designated as emphysematous increased with less negative HU thresholds. The mean lung density in the cohort was $−864 ± 21$ HU and the mean HU threshold below which 15% of the voxels fell was $–946 ± 18$ HU. Finally, the mean total lung score for the visual assessment of emphysema was 16.5 ($± 3.8$), which corresponds to an average score of 3 (50–75%) for each of the six lung zones assessed.

Table 2a provides univariate correlations of measures of pulmonary function to percent emphysema as defined by a range of densitometric HU thresholds. Pearson correlation coefficients and their corresponding p values are shown. Weak but statistically significant correlations were found between measures of lung function and the burden of emphysema at all thresholds with some exceptions. These included all HU defined measures of emphysema and the FVC % predicted, the HU of −810 and the DLCO % predicted, and both the FEV_1 % predicted and the FEV_1/FVC ratio using a threshold of −950 HU. Table 2b provides correlations between pulmonary function and the radiologist scoring system, mean lung density and Perc15. Modest but statistically significant correlations are seen with all measures of lung function except for the Forced Vital Capacity (FVC). Figures 2 and 3 illustrate the relationship of percent emphysema on CT scan and the FEV_1 and DLCO expressed as percent predicted. For the regression of percent emphysema on FEV_1 and DLCO percent predicted, the coefficients of determination were 0.036 and 0.078, explaining approximately 4 and 8 percent of the variability in those measures, respectively.

Additional investigation was performed with a HU of −910 to define regional (upper and lower lung zone) emphysema. Using these measures, there was no difference in the strength of the correlation between either the upper or lower zone emphysema and the FEV_1 % predicted (R = −0.14, $p < 0.0001$; R = −0.15, $p <0.0001$, respectively). Lower zone emphysema was a stronger predictor of the FEV_1/FVC ratio (R = −0.21, $p <$
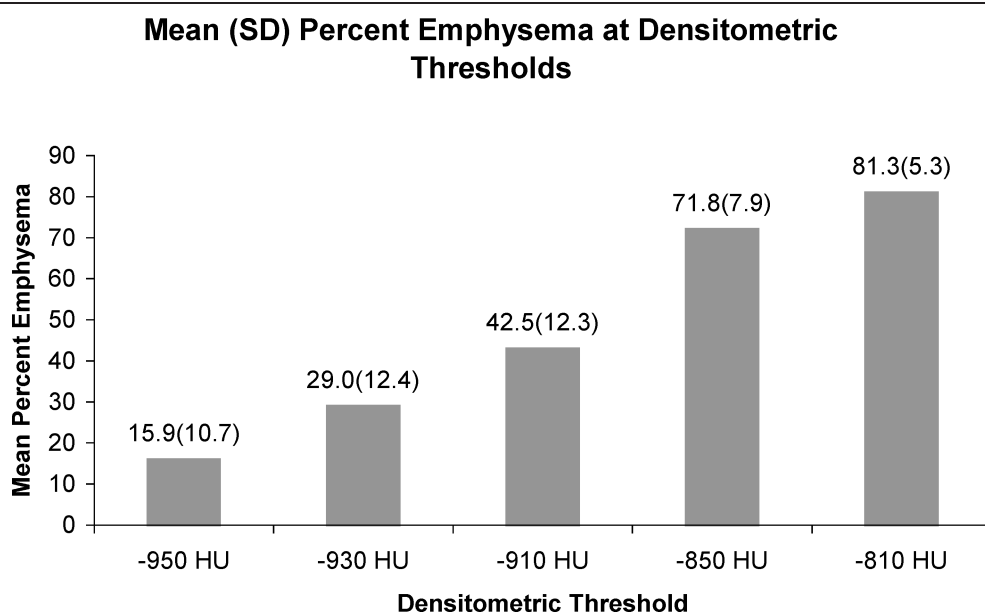

Figure 1. Mean (SD) percent emphysema calculated for the whole lungs using a range of HU thresholds.

Table 2.a. Univariate correlations of measures of pulmonary function and percent emphysema as defined by a range of HU density mask thresholds

| | Emphysema Threshold (Hounsfield Units) | | | | |
	−950	−930	−910	−850	−810
FEV$_1$% (p)	−0.09 (0.004)	−0.15 *	−0.20 *	−0.23 *	−0.22 *
FVC % (p)	−0.01 (0.72)	−0.04 (0.24)	−0.05 (0.07)	−0.07 (0.02)	−0.07 (0.02)
FEV$_1$/FVC (p)	−0.09 (0.004)	−0.15 *	−0.19 *	−0.22 *	−0.21 *
RV % (p)	0.26 *	0.33 *	0.37 *	0.39 *	0.37 *
TLC % (p)	0.23 *	0.30 *	0.35 *	0.39 *	0.38 *
RV/TLC (p)	0.18 *	0.20 *	0.21 *	0.18 *	0.16 *
DLCO % (p)	−0.28 *	−0.30 *	−0.28 *	−0.16 *	−0.10 (0.002)

p values are provided in parenthesis. An asterisk (*) denotes a *p* value < 0.0001.

Table 2.b. Univariate correlations of measures of lung function and the CT burden of emphysema as assessed by the radiologist visual score, and objective measures of mean lung density and the Hounsfield Unit threshold that defines the lowest 15% of lung field attenuation (perc15)

|	Radiologist HRCT Score	Mean Lung Density (HU)	Percent 15 (HU)
FEV$_1$% (p)	−0.09 (0.004)	0.18*	0.09 (0.003)
FVC % (p)	0.03 (0.27)	0.03 (0.36)	−0.01 (0.63)
FEV$_1$/FVC (p)	−0.15 *	0.21*	0.12*
RV % (p)	0.14 *	−0.35*	−0.24*
TLC % (p)	0.14 *	−0.34*	−0.23*
RV/TLC (p)	0.10 (0.0001)	−0.13*	−0.11 (0.0002)
DLCO % (p)	−0.28 *	0.17*	0.23*

p values are provided in parenthesis. An asterisk (*) denotes a *p* value <0.0001.

0.0001 and R = −0.11, *p* = 0.0001, respectively) while upper zone emphysema was more strongly correlated with a subject's diffusing capacity expressed as a percent predicted (R = −0.27, *p* <0.0001; R = −0.11, *p* = 0.0005).

Finally, in an attempt to directly compare the various methods of objectifying the CT based burden of emphysema, univariate regression was performed between each of the densitometric measures of emphysema (HU thresholds, perc15, and mean lung density) and the radiologist scoring system. The strongest correlation between the densitometric thresholds and the radiologist score occurred with a HU threshold of −930 (R = 0.37, *p* <0.0001). There was an inverse relationship observed between the visually determined burden of emphysema and both the perc15 (R = −0.34, *p* <0.0001) and the mean lung density (R = −0.27, *p* <0.0001).

In the subset of 225 subjects with corresponding lung mechanics measurements, a HU threshold of −910, the mean lung density, Perc15, and radiologist visual scoring system were used
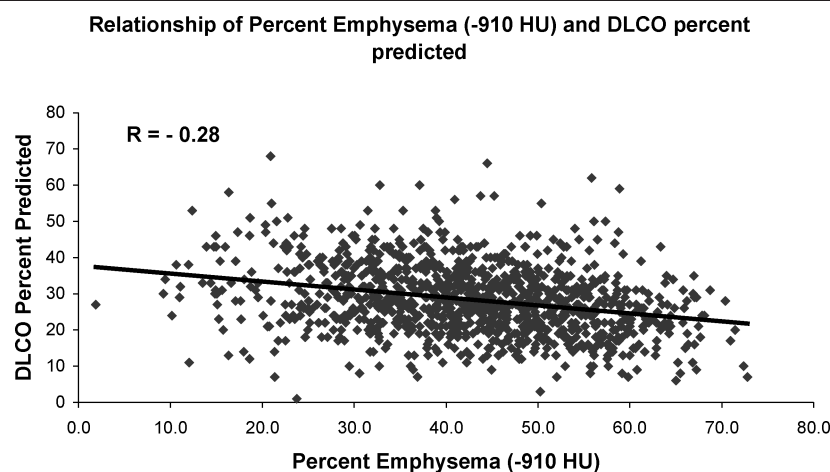

Figure 2. Relationship of FEV$_1$ percent predicted and percent emphysema using a density threshold of −910 HU.
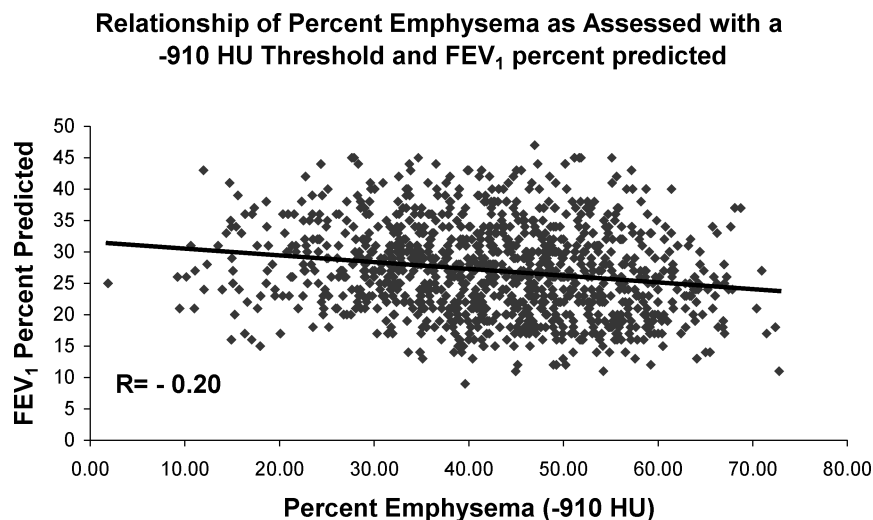
Figure 3. Relationship of DLCO percent predicted and percent emphysema using a density threshold of -910 HU.

to explore the relationship of the burden of emphysema and lung static recoil at total lung capacity. Subject characteristics for the cohort with lung mechanics data were similar to that of the group as a whole and are provided in Table 3. There was no significant relationship between any of these metrics and lung static recoil as assessed with an esophageal balloon ($R = 0.03$, $p = 0.67$; $R = -0.05$, $p = 0.48$; $R = -0.03$, $p = 0.62$; $R = 0.05$, $p = 0.48$ for a HU threshold of -910, mean lung density, Perc15, and the radiologist scoring system respectively). The relationship of the visual scoring system and lung static recoil is further depicted visually in Figure 4.

DISCUSSION

In this investigation, several methods were employed to assess the burden of emphysema apparent on CT scan including semi-quantitative visual interpretation and objective densitometric measurements. These were found to be of modest correlative value for selected univariate measures of pulmonary function but

Table 3. Characteristics of subjects that had pulmonary function measurements, corresponding CT scans, and lung mechanics measurements at time of enrollment

Subject Characteristic	Mean (SD)
Female	101 (45%)
Male	124 (55%)
Age	66.3 (+/− 6.3)
Static Recoil (cmH$_2$O)	8.6 (+/− 3.9)
FEV$_1$ % predicted	27.0 (+/− 7)
FVC % predicted	68 (+/− 15)
FEV$_1$/FVC	0.32 (+/− 0.06)
TLC % predicted	128 (+/− 15)
RV % predicted	219 (+/− 49)
RV/TLC	0.64 (+/− 0.09)
DLCO % predicted	27 (+/− 9)

Post-bronchodilator pulmonary function measurements are reported (n = 225).

poorly correlated of the lung static recoil. With all methods, the strongest correlations were found with those lung function tests that measured lung hyperinflation: RV and TLC. Correlations of a similar magnitude were found with the DLCO. Weaker correlations were found with the spirometric measures of function FEV$_1$, FVC, and FEV$_1$/FVC with the weakest being the FVC percent predicted. Regional measures of emphysema proved to be no better than whole lung measures of emphysema for correlative analysis however as shown previously, lower lung zone emphysema was more strongly associated with measures of airflow obstruction while upper zone disease was more strongly correlated with measures of gas exchange (23).
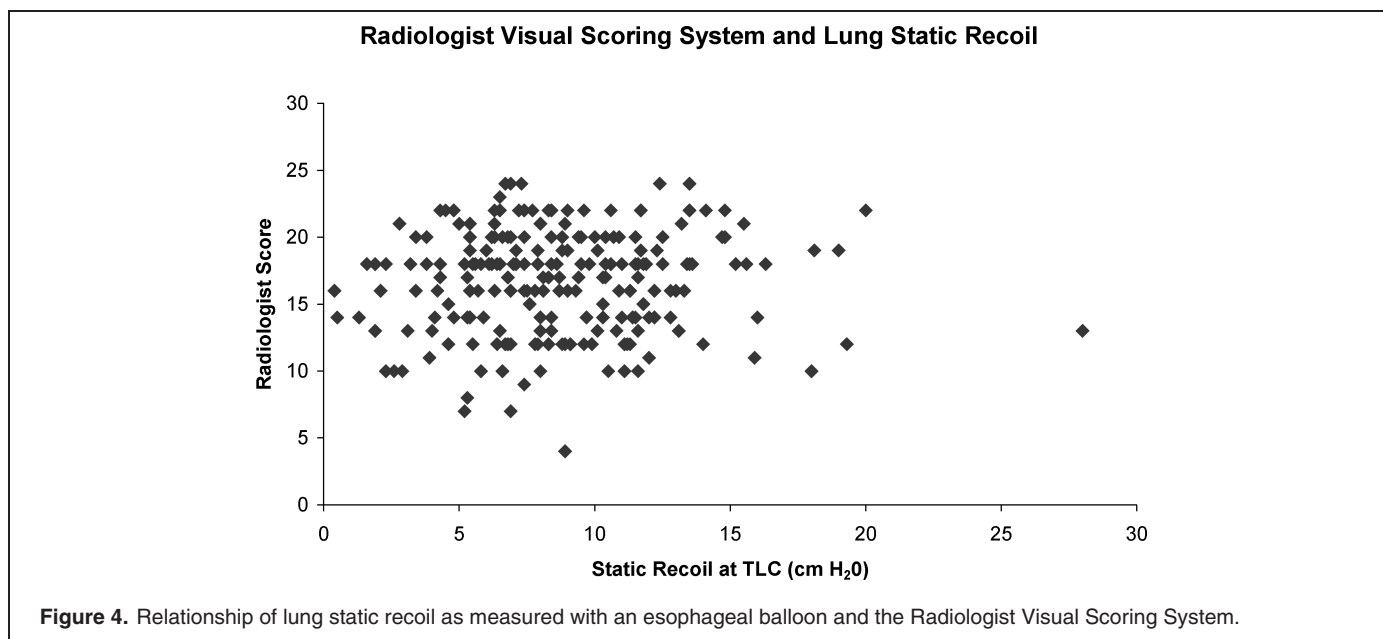
A range of HU thresholds (-810 to -950) were employed in the densitometric quantification of emphysema including the -910 HU believed to be an optimal choice for analysis given the reconstruction of the scans in this investigation (6). While visual inspection of Table 2 reveals a trend of increasing correlation coefficients with less negative HU thresholds, the strength of these correlations was modest in all cases. Interestingly, the trend in the strength of correlations between the HU thresholds and the DLCO was opposite that of all other univariate measures with the magnitude of the coefficients of determination (R^2) increasing with more negative HU values. The reason for this observed trend is unclear.

Similar correlative studies were performed with measures of pulmonary function and the HU threshold that defined the lowest 15% of lung volume, the Perc15. While it is essentially the reciprocal to the HU thresholding (rather than having the HU threshold determine the percent emphysema, the percent emphysema defines the HU threshold), it may offer some advantages over conventional densitometric thresholding. Prior publications have suggested that in certain regions of the lung density histogram, densitometric thresholding may be insensitive to the burden of emphysema, a property not shared by the Perc15 (24). Because of this, the Perc15 may be more sensitive for the detection of disease progression and may be a more useful tool for correlative studies (19). In this investigation, the

Radiologist Visual Scoring System and Lung Static Recoil

Figure 4. Relationship of lung static recoil as measured with an esophageal balloon and the Radiologist Visual Scoring System.

Perc15 was comparable to densitometric thresholding in its ability to predict lung function with the univariate coefficients of determination being closest to those found with a HU threshold of −950.

The final automated densitometric measure of emphysema employed in this investigation was the Mean Lung Density. While prior investigations have reported correlations between the MLD and measures of lung function, this metric has significant limitations. It is quite sensitive to image noise and has been found to be less sensitive to changes in lung density than other automated methods (25). Because of this, it is not an optimal tool for the assessment of parenchymal disease progression. In the present investigation, MLD was found to be of similar predictive value for measures of lung function and did not clearly outperform the Perc15 or the densitometric thresholding methods.

The visual grading of HRCT images by the study radiologists proved to be inferior to densitometric analysis for correlation with most measures of lung function. These results must be interpreted with some caution since the visual scoring was performed on the higher resolution images while the automated densitometric methods utilized the standard clinical reconstructions. As reported with densitometric thresholding methods, this difference in reconstruction algorithms is systematic in its influence on the burden of emphysema apparent on the images (26).

Higher-resolution reconstruction algorithms have been reported to increase the fraction of emphysematous lung for a given Hounsfield Unit threshold. Consistent with this observation is the higher mean burden of emphysema determined by visual as compared to densitometric methods. This effect should, however, be systematic and therefore should not significantly influence analysis. It is more likely that the subjectivity of the visual quantification methods, specifically the inter-observer variability in scoring had a significant impact on the strength of these correlative measures.

The lack of a correlation between the burden of emphysema apparent on CT scan and static recoil supports previous observations made by Baldi et al., and may in part be due to the limitations of the currently available imaging technology (27). While the standard anatomic definition of emphysema is one of permanent dilation and destruction of the terminal airspaces due to loss of lung parenchyma (28), CT imaging lacks the resolution to directly detect and differentiate such microscopic processes as centrilobular (CLE) and panlobular emphysema (PLE).

Further, it is unclear if the macroscopic pattern of parenchymal destruction apparent on the CT image assessed by automated methods can be used to infer the presence and quantity of these distinct pathologic conditions. Finally, both visual and objective methods for assessing the burden of emphysema do not differentiate emphysematous destruction of the lung tissue and over-expanded lung tissue due to gas trapping. Whereas one is a direct result of parenchymal destruction, the other reflects regional expiratory airflow obstruction that may not be representative of the aggregate burden of lung disease. Such a lack of distinction may in part be responsible for the weak predictive value of "emphysema" and lung function in this study. Additional work is needed to investigate and clarify the ability of quantitative CT scan analysis to predict the presence of these conditions. Given recent published data on the relationship of small airways disease and CLE, one solution may the measurement of the airway wall thicknesses (29).

A surprising finding in this investigation is the wide range of emphysema on CT scan in a study cohort that was selected to have emphysema as their predominant manifestation of lung disease. For example, using a threshold of −910HU to define airspace disease, the burden of emphysema present in the study subjects ranged from 10 to over 70% of the lung. A similar finding is shown when examining the relationship of lung function and percent emphysema (Figure 2). Again, in this investigation, a

subject with an FEV_1 of 25% predicted had between 10 and 70% of their lung defined as emphysema. Such a finding suggests that CT image analysis may be complementary to the phenotyping data obtained through pulmonary function testing. Additional investigation is required to determine if such factors as the type of emphysema, centrilobular or panlobular, and CT based quantitative measures of airway disease would provide further discriminatory data in this cohort.

While the size of the cohort is larger than any previously reported for such an analysis, the relative homogeneity of the lung function within the cohort limits the conclusions that can be drawn. As is outlined in the NETT inclusion criteria, this group consists of subjects with severe ventilatory obstruction and emphysema on CT scan. A second limitation to the investigation is the densitometric tools themselves. Simple dichotomization of the lung into a fraction of healthy and diseased tissue does not differentiate bullous and more homogeneous disease and may not adequately address their unique mechanical impact.

Acknowledging these limitations, while there may be an optimal HU threshold for comparison to histologic specimens, selection of a specific densitometric method for analysis appears to have a limited impact on the strength of the correlations to measures of lung function. Both densitometric analysis and visual inspection of the CT scans proved to be of weak predictive value for function in this investigation. They did however convey potentially valuable information on the burden of parenchymal disease in COPD not readily quantifiable with standard lung function testing. Computed Tomographic imaging is widely available, safe, and can simultaneously provide useful clinical and research based information. The application of such an imaging technique as a biomarker for disease characterization and as an intermediate endpoint for interventional studies requires further studies into the methodology of disease quantification.

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