Quantifying the Extent of Emphysema:

Factors Associated with Radiologists' Estimations and Quantitative Indices of Emphysema Severity Using the ECLIPSE Cohort

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Rationale and Objectives: This study investigated what factors radiologists take into account when estimating emphysema severity and assessed quantitative computed tomography (CT) measurements of low attenuation areas.

Materials and Methods: CT scans and spirometry were obtained on 1519 chronic obstructive pulmonary disease (COPD) subjects, 269 smoker controls, and 184 nonsmoker controls from the Evaluation of COPD Longitudinally to Indentify Surrogate Endpoints (ECLIPSE) study. CT scans were analyzed using the threshold technique (%<−950HU) and a low attenuation cluster analysis. Two radiologists scored emphysema severity (0 to 5 scale), described the predominant type and distribution of emphysema, and the presence of suspected small airways disease.

Results: The percent low attenuation area (%LAA) and visual scores of emphysema severity correlated well ($r = 0.77$, $P < .001$). %LAA, low attenuation cluster analysis, and absence of radiologist described gas trapping, distribution, and predominant type of emphysema were predictors of visual scores of emphysema severity (all $P < .001$). CT scans scored as showing regions of gas trapping had smaller lesions for a similar %LAA than those without ($P < .001$).

Conclusions: Visual estimates of emphysema are not only determined by the extent of LAA, but also by lesion size, predominant type, and distribution of emphysema and presence/absence of areas of small airways disease. A computer analysis of low attenuation cluster size helps quantitative algorithms discriminate low attenuation areas from gas trapping, image noise, and emphysema.

Key Words: Emphysema; chronic obstructive pulmonary disease; computed tomography; quantitative CT; small airways disease.

The introduction of computed tomography (CT) has changed the way that clinicians diagnose and quantify the extent of emphysema in living individuals. It was recognized early on that the frequency distribution of x-ray attenuation values in a CT image of the lung (CT densitometry) could produce an estimate of the extent of emphysema (1–3). Even though there has been a great deal of attention given to densitometric assessment of emphysema (4–8), the daily clinical routine is still to visually grade disease extent and severity.

Both densitometry (1,3,4) and visual grading of emphysema extent (9–11) have been shown to correlate well with the extent of emphysema on histology specimens. However, the estimations produced by densitometry have been reported to be similar to the extent of emphysema in histology specimens, whereas visual estimations tend to overestimate the extent of emphysema (12,13). Visual scores, on the other hand, have been reported to show stronger associations with spirometry data (14), the core diagnostic test to detect and stage chronic obstructive pulmonary disease (COPD) (15).

Another advantage of visual scoring is the ability of radiologists to distinguish emphysema from other causes of lowered attenuation such as image noise and hyperinflated regions

Acad Radiol 2011; 18:661–671

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doi:10.1016/j.acra.2011.01.011

consistent with "gas-trapping" caused by small airways disease. Although densitometry can quantify the spatial distribution of low attenuation voxels, it cannot discriminate other features within the CT scan that may help decide the cause of the low attenuation areas. For these reasons, investigators have attempted to develop new techniques using multiple features within a CT image (16). The most simple of these approaches examines how the low attenuation voxels are clustered together (17,18). Low attenuation areas consistent with gas-trapping and image noise are typically characterized by small clusters of voxels with decreased attenuation, whereas emphysema often results in larger clusters, especially in the advanced stages. Radiologists tend to look for those larger areas of low attenuation areas and use the size of destroyed areas in their estimation of the extent of emphysema, but the use of cluster analysis in computer based quantification of emphysema is limited (17,19,20). Although low attenuation cluster (LAC) analysis alone has been shown not to be able to estimate extent of emphysema (19), we hypothesized that the LAC analysis may be able to help to understand the relationship between densitometry results and visual scores.

The purpose of the current analysis is to investigate the relationship between densitometry results and visual scores by assessing factors that determine estimations of emphysema extent as seen by radiologists. To accomplish this we used the baseline CT scans from the Evaluation Of COPD Longitudinally To Identify Predictive Surrogate Endpoints (ECLIPSE) (NCT00292552; GSK Study Code SCO104960) cohort, which is a large cohort of smoking and nonsmoking subjects with and without airflow limitation (21–23).

MATERIAL AND METHODS

Subjects

The ECLIPSE Study is a 3-year noninterventional longitudinal study designed to discover and validate novel and robust metrics of disease and disease progression (23). The trial was approved by the ethics and review boards at participating centers and written informed consent was obtained from all subjects. A list of all participating centers can be found in Appendix 1. Individuals ages 40 to 75 years were recruited to the COPD study group if they had a smoking history of ≥10 pack-years, a postbronchodilator forced expiratory volume in 1 second (FEV_1) less than 80% predicted, and a postbronchodilator ratio between FEV_1 and forced vital capacity (FVC) ≤0.7. Smoking (≥10 pack-years) and nonsmoking (<1 pack-year) control subjects were enrolled if they were ages 40 to 75 years and had normal lung function (postbronchodilator FEV_1>85% predicted and FEV_1/FVC >0.7). Individuals recruited to the study were genotyped for α_1-antitrypsin deficiency and six homogenous protease inhibitor variant Z (PiZZ) and 11 heterozygous variants SZ (PiSZ) individuals were identified and excluded from the analysis (24).

Pulmonary Function Testing

Postbronchodilator spirometry (ie, FEV_1 and FVC) was performed following the American Thoracic Society guidelines. Subjects were asked to withhold bronchodilator medication for at least 6 hours before testing. For descriptive purposes, COPD subjects were staged according to GOLD guidelines (15).

CT and Quantitative Analysis (Densitometry)

CT scanning was performed without bronchodilatation within 1 day of lung function testing. All CT scans were acquired using multidetector-row CT scanners (GE Healthcare, Milwaukee, WI or Siemens Healthcare, Erlangen, Germany) with a minimum of four rows at suspended full inspiration without administration of intravenous contrast. Exposure settings were 120 kVp and 40 mAs; images were reconstructed using 1.0 mm (Siemens) or 1.25 mm (GE) contiguous slices and a low spatial frequency reconstruction algorithm (GE: standard; Siemens: b35f) at a 512 × 512 matrix. All CT scans were analyzed using Pulmonary Workstation 2.0 software (VIDA Diagnostics, Iowa City, IA). Lungs were segmented from the thoracic wall, the heart, and main pulmonary vessels, followed by segmentation of the individual lobes and the airways (25). The extent of emphysema was estimated using the threshold technique quantifying the percent of voxels with an apparent x-ray attenuation value below −950 HU (%LAA) (5). The size of the emphysematous lesions was estimated using a LAC analysis (17,18). In short, the cumulative size of the lesion (the number of connected low attenuation voxels) is plotted against the cumulative number of lesions (clusters of a given size) on a log-log scale. The slope of this relationship, the power law exponent (D), is an indication of average lesion size: The steeper the slope, the smaller the lesions.

Qualitative Analysis (Visual Scoring)

All images were displayed on a standalone medical imaging workstation (eFilm 3.0, Merge Healthcare, Milwaukee, WI), enabling the readers to view the images in different planes and using a standard window width of 1000 and a window level of −700 HU. The qualitative analysis was performed on images obtained using high spatial frequency reconstruction algorithm (GE: bone; Siemens: b60f). Emphysema was visually scored by two experienced chest radiologists, who independently scored all CT scans as follows: 0 = no emphysema, 1 = <5% (trivial), 2 = 5–25% (mild), 3 = 26–50% (moderate), 4 = 51–75% (severe), and 5 = >75% involvement of both lungs (very severe). In case of disagreement, the mean score of the two readers was used as the final score (0.5, 1.5, 2.5, 3.5, or 4.5) unless the results differed more than one category. For those cases consensus was reached in a separate reading session and that score was used. The distributions of emphysema, if present, was described as upper lobe predominant, lower lobe predominant or diffuse emphysema; and the predominant type of