Repeatability of Lung Density Measurements with Low-Dose Computed Tomography in Subjects with α-1-Antitrypsin Deficiency–Associated Emphysema


RATIONALE AND OBJECTIVES. Multislice computed tomography (MSCT) of the lungs provides a new opportunity for longitudinal assessment of lung densities because of shorter scan duration. The aim of the present study was to assess the intraindividual variation of lung densities measured by MSCT of patients with emphysema.

METHODS. Ten patients with emphysema participated in a study in which MSCT was obtained on two occasions, approximately 2 weeks apart. Scanning parameters were 140 kV, 20 mAs, 4 × 2.5-mm collimation, and effective slice thickness of 2.5 mm. Lung density was measured as the 15th percentile point and the relative area below 910 Hounsfield units (HU) by using Pulmo-LKEB software.

RESULTS. The mean difference of the 15th percentile point was −1.29 ± 3.2 HU, and that for the relative area below the −910-HU parameter was −1.02% ± 3.09%. Intraclass coefficients of variation were 0.96 (0.86–0.99) and 0.94 (0.8–0.98), respectively (95% confidence interval).

CONCLUSIONS. Lung density parameters of emphysema derived by MSCT provide an opportunity for analysis of the treatment effects of new drugs on the progression of emphysema.

KEY WORDS. Emphysema; computed tomography; lung densities.

TRADITIONALLY, the extent of emphysema of patients is measured by pulmonary function tests such as forced expiratory volume in 1 second (FEV₁) and carbon monoxide diffusion capacity, in combination with visual assessment of the lung parenchyma by computed tomography (CT). To date, the progression of emphysema is measured by FEV₁, and studies of the efficacy of new drugs are usually based on the annual decline of FEV₁.¹² Power calculations for such studies result in trial designs for periods of more than 3 years, with 300 or more patients.

Many studies have shown that the extent of emphysema measured by pathology scores in resected lung tissue is well correlated with lung density values obtained from preoperative CT of the lung.³⁴ In 1988, Gould et al³ were the first to use lung density measures in a quantitative fashion by using the histogram obtained in vivo before surgical resection of a lung lobe. Furthermore, their pathological quantitative scoring of emphysema was unique because it related a measure of air space wall to unit of lung volume. In 22 specimens, they found a highly significant correlation of 0.77 between CT lung density and the pathology score. Bankier et al⁴ showed in 56 specimens a highly significant correlation of 0.62 between the CT emphysema score (RA₉₅₀) and a score of microscopic emphysema. In these studies, similar correlations were found between carbon monoxide diffusion capacity and pathology scores. These observations have led to the hypothesis that longitudinal measurements of lung density may be more sensitive to assess the progression of emphysema than are pulmonary function tests.⁵
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Absolute (mean ± SD)</th>
<th>% Pred. (mean ± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>7/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>50 ± 7</td>
<td></td>
<td>37–61</td>
</tr>
<tr>
<td>Smoking (pack-y)</td>
<td>20.0 ± 2.39</td>
<td>41 ± 16</td>
<td>10–35</td>
</tr>
<tr>
<td>FEV1 (mL)</td>
<td>1300 ± 438</td>
<td>41 ± 16</td>
<td>22–69 (% pred)</td>
</tr>
<tr>
<td>KCO (mL · min⁻¹ · mm Hg⁻¹ · L⁻¹)</td>
<td>0.82 ± 0.19</td>
<td>54 ± 12</td>
<td>33–76 (% pred)</td>
</tr>
</tbody>
</table>

SD: indicates standard deviation; differences were considered significant at P < 0.05. Repeatability was expressed as the intraclass correlation coefficient (between-

With the recent introduction of multislice CT (MSCT) scanning, shorter scanning times and lower radiation exposure provide a new challenge for lung density measurements as new outcome parameters for the efficacy of drugs in patients with emphysema. No data on the repeatability of lung densitometry in patients with emphysema are, however, available in the literature. Such data would give insight into the variability one might expect during the assessment of changes in lung density over time with this new technology. Therefore, the aim of the current study was to determine the repeatability of lung density measurements in patients with various degrees of α-1-antitrypsin deficiency--associated emphysema.

Methods

Patients and Study Design

Ten patients with α-1-antitrypsin deficiency of the Pi-Z phenotype and with a diagnosis of emphysema were studied. Informed consent was obtained from all subjects after approval by the ethics committee. Patient characteristics are shown in Table 1. Pulmonary function testing was performed according to European Respiratory Society recommendations. Patients were in stable clinical condition, and none were receiving α-1-antitrypsin replacement therapy.

All patients underwent two CT scans of the chest 2 weeks apart, with a pulmonary function test on the day of the second CT scan. The CT scans were performed in two different hospitals (Rotterdam and Brussels) on the same type of scanner. One hour before the CT scan, patients took 400 μg salbutamol as a bronchodilator.

Computed Tomography Scans

Both CT scans were performed in the supine position with the Siemens Volume Zoom MSCT scanner (Siemens, Erlangen, Germany). No contrast medium was used. Scans were obtained during full inspiration after three deep inhalation maneuvers. Images were obtained in a caudocranial direction to avoid breathing artifacts at the level of the diaphragm. The CT settings were 140 kV, 40 mA (20 mAs), rotation time 0.5 second, pitch 7, 4 × 2.5-mm collimation, effective slice thickness 2.5 mm, and reconstruction increment 2.5 mm. With these settings, a chest of 30 cm can be imaged in 8 to 9 seconds. The images were reconstructed with a high filter (B30).

Image Analysis

All CT scans were analyzed by using a software package as described previously. Basically, the analysis of the CT data consists of four steps: blood calibration; automatic segmentation of the lungs in three dimensions, allowing assessment of the volume of the lung at the inspiration level held by the patient during scanning; calculation and subsequent analysis of the density distributions; and presentation of the measurement results. The histograms of the left and right lung were calculated from the CT data. From these histograms, parameters such as total lung volume, mean lung density, the n-th percentile point, and the area of the lungs (in percent) below a certain density value, called the relative area, were calculated.7 The mean lung density and the lung volume allow the calculation of the lung weight by multiplying these two values. The n-th percentile point is calculated from the frequency distribution of the densities and is defined as the density value (in Hounsfield units [HU], or g/L) at which n% of the pixels have a lower density. In a previous study, percentile parameters of the histogram in the range from 1% to 50% were evaluated, and percentiles in the range from 10% to 20% were found most pertinent because they showed the strongest time trend in a longitudinal study of lung density assessment in emphysema. Therefore, the 15th percentile point was chosen as the effect variable of the present study for the whole lung because it previously showed the lowest variation.3 The relative area below −910 HU (RA −910) is defined as the relative number of pixels within the lungs with a density below the threshold of −910 HU. This type of parameter, though with various thresholds, is frequently used in studies assessing correlations between pathology and CT scanning of the lung.4 All CT densitometric parameters were standardized by logarithmically transformed lung volume to correct for differences in lung volume between scans, as reported previously.8

Statistical Analysis

Differences in lung density parameters between the two acquisitions were analyzed in SPSS (SAS Institute Inc., Cary, NC) with Student’s t test for paired data. The data are expressed as mean ± standard deviation; differences were considered significant at P < 0.05. Repeatability was expressed as the intraclass correlation coefficient (between-
been validated in a previous study. Although patients were from a mixed population with various pulmonary conditions. The Lung Health Study reported that the coefficient of variation of FEV1 was 4%, similar to results from the Copenhagen Heart study. We calculated from their results that the correlation coefficient of variation was 0.93. In multicenter studies, the FEV1 had an intraclass correlation coefficient of variation for the whole group. Table 2 shows the effect of correction for differences in lung volumes of the two scans on each of the density parameters. The intraclass correlation coefficient of variation for the 15th percentile point, corrected for differences of total lung volume between the two scans, was 0.96 (0.86–0.99); that for RA-910 was 0.94 (0.8–0.98) (95% confidence interval). Calculated values of lung weights and mean lung density are also summarized in Table 2. The intraclass correlation coefficient of lung weight, corrected for total lung volume of the lung, was 0.99 (0.98–0.99); that for mean lung density was 0.93 (0.77–0.98).

**Discussion**

Our results show excellent repeatability of quantitative lung density analysis in subjects with emphysema. Factors related to CT, differences in the use of the software, or patient characteristics could have influenced the repeatability of our results. The variation between CT scanners at different sites was minimal; both machines were quite new and differed by only 10 months in age. All other technical aspects of the scanners and their software were identical. Lung density measurements were made with one software package that automatically detects lung contours and has been validated in a previous study. Although patients were scanned in a stable clinical condition, there were marked differences in disease severity between patients, as indicated in Table 1. Therefore, we suggest that patient characteristics were the main source of variation in the lung density measurements. One aspect of the patient-related variation in lung density is caused by the volume of the lungs during full inspiration. During each scan patients were instructed to hold their breath at full inspiration. Table 2 shows that total lung volume measured by CT did not vary much between the two CT scans and indicates that standardization with lung volume data can improve the reproducibility of the measurement.

In previous studies, lung densities were measured in a cross-sectional design, and results were compared with pathological scores or with carbon monoxide diffusion capacity. Both showed significant correlations, ranging between 0.6 and 0.8. Few studies have reported on the reproducibility of lung densitometry in a clinical setting. Lamers et al. found that lung densities in 1-mm slices at 5 cm above and below the tracheal carina were most reproducible when the patients were scanned during spirometrically gated 90% of vital capacity. No correlation coefficient or percent coefficient of variation, however, was reported, and therefore, the variations in the measurement were not related to the variations between subjects. Furthermore, these patients were from a mixed population with various pulmonary conditions.

Recently, we reported that longitudinal lung density measurements are more sensitive for the detection of progression of emphysema than is FEV1 or diffusion capacity. To date, the FEV1 is regarded as one of the most reproducible tests for obstructive lung disease. The Lung Health Study reported that the coefficient of variation of FEV1 was 4%, similar to results from the Copenhagen Heart study. We calculated from their results that the correlation coefficient of variation was 0.93. In multicenter studies, the FEV1 had a standard deviation within subjects between 100 and 150 mL. This is quite a large measurement variability compared with the annual decline in FEV1, which is ±30 mL in normal adults and ±60 mL in those with α1-antitrypsin deficiency. Multiple factors such as loss of elastic recoil and small-airway disease influence the result of these FEV1 measurements as opposed to CT densitometry. The variability of repeated measurements of single-breath diffusing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean difference, lung volume (uncorrected/corrected)</th>
<th>SD of the difference, lung volume (uncorrected/corrected)</th>
<th>P value, paired t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>−24.45/−22.66</td>
<td>17.8/18.1</td>
<td>0.07</td>
</tr>
<tr>
<td>MLD (HU)</td>
<td>4.50/4.30</td>
<td>8.53/8.38</td>
<td>0.12</td>
</tr>
<tr>
<td>Perc15 (HU)</td>
<td>0.28/−1.29</td>
<td>4.33/3.24</td>
<td>0.17</td>
</tr>
<tr>
<td>RA-910 (%)</td>
<td>−1.88/−1.02</td>
<td>3.92/3.19</td>
<td>0.12</td>
</tr>
</tbody>
</table>

MLD indicates mean lung density; Perc15: 15th percentile; RA-910: relative area below −910 Hounsfield units (HU).
capacity is greater than that of FEV$_1$, and therefore, it has less potential as a progression parameter.

Obviously, a disadvantage of the use of CT for monitoring the progress of emphysema is the radiation exposure to the patient. We calculated that the radiation exposure during each multislice volume scan was 0.7 mSv for a chest of 30-cm length, which is well below the annual background exposure (2 mSv). This low dose is accomplished by the low mA setting in our acquisition protocol. For comparison, a standard CT protocol yields an exposure of 6 to 10 mSv. Our protocol results in exposures well within the recommended range of annual exposure (1–10 mSv) for biomedical studies with an intermediate risk.\(^\text{11}\)

We conclude that our lung density measurements show equal repeatability to FEV$_1$ and relatively small standard deviations. On the basis of our previous findings in a longitudinal study,\(^\text{12,13}\) we also recommend the use of lung density parameters as end points in the future evaluation of new drugs for emphysema.

**Acknowledgments**

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**References**


