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## Evaluating Qualitative and Quantitative Computerized Tomography Indicators of Chronic Obstructive Pulmonary Disease and Their Correlation with Pulmonary Function Tests

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### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

### Summary

#### Background:

With increasingly aging populations, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death today. Emphysematous changes, an important component of the disease, must be determined on HRCT, either qualitatively or quantitatively. The purpose of this study was to evaluate features that help determine emphysematous changes and correlate them with respiratory function tests (RFTs).

#### Material/Methods:

A total of thirty COPD patients and a control group of the same size, matched for age, were included in the study. The mean lung parenchyma density values on inspiration and expiration, visual HRCT scores, and pulmonary function tests were obtained. IBM SPSS statistical software (version 22) was used to perform correlation analysis (Pearson's coefficient) and the Mann-Whitney U test.

#### Results:

The most valuable RFTs for determining emphysematous changes were DLCO, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC, in that order. Quantitative measures of the mean lung density had the highest correlation with coefficient on expiration.

#### Conclusions:

As regards the comparison between objective and subjective density values, the HRCT-based visual density values are satisfactory. On the other hand, the best assessment can be performed with the use of mean density values on expiration. DLCO, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC were found to be valuable parameters in determining parenchymal changes.

#### MeSH Keywords:

Pulmonary Disease, Chronic Obstructive • Respiratory Function Tests • Tomography, Spiral Computed

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### Background

COPD is a well-defined disease. In many countries, its incidence tends to rise. Because the lungs are among the early aging organs, in recent years, researchers have identified this disease primarily among the elderly. However, in the industrialized world, other factors, such as environmental pollution, stressful life, and long-term tobacco use, must be considered as additional causes [1,2].

In previous years, the course of the disease used to be determined by the forced expiratory volume in the first second (FEV<sub>1</sub>). The reason for that was the assumption that the development of symptoms was due to air flow restrictions [3].

After developing a comprehensive database, Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined a guideline for COPD treatment, which was additionally based on the severity of symptoms and future risk of aggravation [4].

High-resolution computed tomography (HRCT) can help to evaluate the involved components of the lungs and severity of the disease. For instance, qualitative assessment of emphysematous changes has a satisfactory correlation with airflow obstruction [5–7]. On the other hand, objective measures of airway wall thickening also correlate well with pulmonary function [7–9]. Which features of specific lung structural abnormalities (emphysema, airway wall thickening, bronchiectasis, or nodularity) may provide a meaningful foresight to clinical course is still not clear [10].

There are some articles that compare quantitative CT visual assessment with several physiological parameters; both measure types have a good correlation [11]. For instance, Kitaguchi et al. [12] used a visual evaluation of CT to phenotype COPD patients, which allowed for the identification of subgroups of patients with different clinical and functional characteristics.

The aim of the present study was to evaluate the distribution of emphysematous changes with qualitative visual scores, functional tests, and quantitative methods (HRCT) in patients with COPD.

## Material and Methods

Thirty patients with clinically diagnosed COPD, randomly selected, and with stable disease were enrolled, along with thirty normal individuals with no clinical symptoms. Twenty-nine patients were male and one patient was female. Age ranged between 41–72 years. All patients were smokers, and on average, they had 35 pack-years of smoking. The control group consisted of thirty healthy individuals (12 men, 18 women) with normal pulmonary function. Age ranged between 39–74 years. None of controls was a smoker.

HRCT scans were obtained within 2 weeks after pulmonary function tests. The examination was performed by with the Philips Ingenuity Core 128 device. Axial slices were obtained on deep inspiration and on expiration. Sections were acquired at three levels, as follows, 1 cm above the upper contour of the aortic arch, 1 cm below the carina, and 3 cm above the diaphragm dome. The matrix was 512×512, slice thickness was 1 mm.

The kV value was 120, and mA was 80–281. A bone reconstruction algorithm was used. Intravenous contrast agents were not used.

### Image analysis

Observers were unaware of the clinical data and pulmonary function tests, while evaluating visual data. Slices were evaluated by two radiologists simultaneously. Six pulmonary parenchymal areas were evaluated from three different anatomic levels for each patient.

The emphysema score was calculated by multiplying severity and prevalence.

The final score was determined as the mean score of the two observers (radiologists).

The severity of emphysema was evaluated qualitatively based on four scores:

- 0 – No emphysema;
- 1 – Low attenuation areas, 5 mm or smaller (with or without vascular interruption);
- 2 – Low attenuation areas larger than 5 mm;
- 3 – Low attenuation areas without safe lung parenchyma (could be accompanied by vascular distortion and interruption).

The extent of emphysema was determined on four levels:

- 1 point: lower than 25%;
- 2 points: 25–50%;
- 3 points: 50–75%;
- 4 points: over 75%.

Emphysema scores were calculated by multiplying the severity and extent of disease for each six lung areas. After adding six scores of the lung fields, a total HRCT emphysema visual score was obtained (ranging between 0–72 points).

Average density values were measured for each largest lung area, with exclusion of central bronchovascular areas, in order to make possible a quantitative determination on deep inspiration and expiration. The average value of six density values was calculated for each slice.

Respiratory function tests were performed with the use of the SensorMedics 2400–2440 device.

### Respiratory function tests

Forced expiratory volume in the first second (FEV<sub>1</sub>%), forced vital capacity (FVC), vital capacity (VC), total lung capacity (TLC), forced residual capacity (FRC), and residual volume (RV) were used as respiratory function tests. Normal values were determined according to the criteria of the American Thorax Society (ATS).

After obtaining all data, correlation analysis was performed between visual CT scores, average density values, and respiratory function tests.

### Statistical analysis

IBM SPSS statistical software (version 22) was used to perform correlation analysis (Pearson's coefficient) and the Mann-Whitney U test.

### Ethical statement

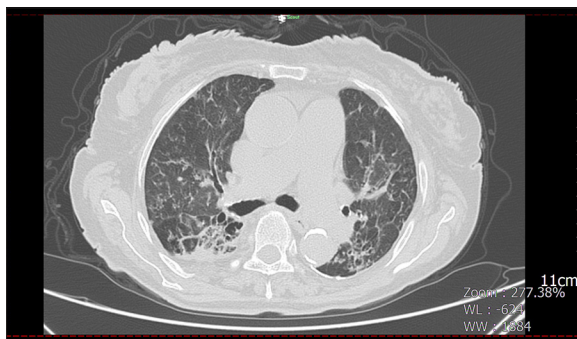
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent

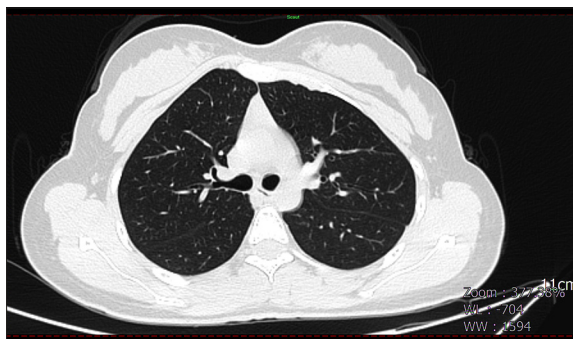
Informed consent was obtained from all individual participants included in the study.

**Table 1.** Mean RFT of patients

RFT	N	Mean	Standard deviation	Min–Max
DLCO	17	64.29	37.78	22–140
FVC	27	64.41	24.72	31–122
VC	26	66.69	20.90	32–117
TLC	17	92.06	14.31	65–112
FRC	17	123.00	24.89	77–165
RV	17	145.71	39.73	78–247



**Figure 1.** A patient with COPD. Age: 62; HRCT visual emphysema score: 4 (for the level 1 cm below the carina); Visual emphysema score: 14 (in total).



**Figure 2.** A normal individual from the control group. Age: 41; HRCT visual emphysema score: 0 (for the level 1 cm below the carina); Visual emphysema score: 0 (in total).

## Results

The mean age of patients was 48.3 years, and the mean age of the control group was 47.9 years.

Based on the ATS criteria, mild airway obstruction was found in 3 patients, moderate obstruction in 12, and severe obstruction in 10 patients. In 5 patients, the results were within normal limits. The results of the respiratory function tests, for the patient group, are shown in Table 1.

The HRCT visual score was between 12–67 points in patients, and between 0–5 points in the control group.

Figure 1 shows a 62-year-old patient with COPD.

HRCT visual emphysema score: 4 (for the level 1 cm below from the carina).

Visual emphysema score: 14 (in total).

Figure 2 shows a 41-year-old normal individual from the control group.

HRCT visual emphysema score: 0 (for the level 1 cm below from the carina).

Visual emphysema score: 0 (in total).

The mean visual score of patients and controls was 33.5 and 2.4 points, respectively. The difference in the mean HRCT visual score between patients and controls was statistically significant ( $p < 0.01$ ).

There was a statistically significant negative correlation between HRCT visual scores and FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and DLCO values; a positive correlation between HRCT visual scores and FRC values was also seen (Table 2).

The correlation coefficient between HRCT visual scores and the mean density values on inspiration was 0.66, and 0.76 on expiration.

The difference between the mean density values on inspiration and on expiration was decreased in patients with airway obstruction, in comparison to the control group; this difference was statistically significant (Table 3).

Correlation coefficients between RFTs and density values on inspiration and on expiration, and HRCT visual scores are presented in Figure 3.

## Discussion

The lungs are among the fastest aging organs. The most commonly used RFTs are FEV<sub>1</sub>, FVC, VC, FRC, TLC, and RV. After the age of 20 years, FRC and RV tend to increase, and FEV<sub>1</sub>, FVC, VC, and TLC tend to decrease. With increasing age, mostly interstitial but also alveolar parenchymal changes can be determined on HRCT. Consequently, without the presence of any disease, age alone can cause parenchymal (density) changes in the lungs. Therefore, the mean age of COPD patients and that of the control group was similar in our study.

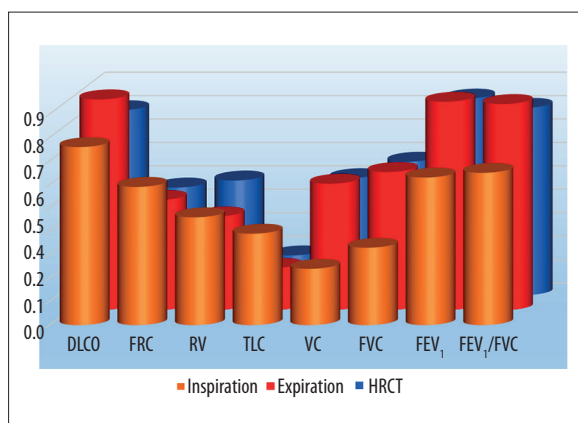
Many studies have shown that CT is a reliable method for demonstrating parenchymal changes specific for

**Table 2.** The relation between RFT values and mean density, visual HRCT score of patients .

RFT	Inspiration	Expiration	P	HRCT visual correlation
DLCO	-0.76	-0.90	<0.01	0.79
FRC	0.59	0.47	0.015	0.46
RV	0.46	0.40	0.07	0.49
TLC	0.39	0.18	0.13	0.17
VC	-0.24	-0.54	0.27	-0.50
FVC	-0.33	-0.59	0.104	-0.57
FEV <sub>1</sub>	-0.63	-0.89	<0.01	-0.84
FEV <sub>1</sub> /FVC	-0.65	-0.88	<0.01	-0.80

**Table 3.** Mean inspiration and expiration density values of patients as Hounsfield unit values.

	Patients		Control		U value	P
	Mean	Std dev.	Mean	Std dev.		
Inspiration	853.97	24.04	890.90	28.82	49.0	<0.01
Expiration	860.44	50.29	696.08	59.37	9.0	<0.01

**Figure 3.** Correlation coefficients between RFTs and density values on inspiration and expiration as well as HRCT visual scores.

emphysema. Some authors argue that CT is even more effective than pulmonary function tests. CT has a sensitivity of approximately 96% in diagnosing emphysema and can detect emphysematous areas as small as 0.5 cm<sup>2</sup> [12–15]. Two main methods are currently used to determine lung parenchyma changes on CT. One is visual determination, and the other is quantitative measurement of lung parenchyma density.

The most important disadvantage of visual evaluation is that it is subjective and can be influenced by observer's experience, CT window properties, and inter-observer variability. On the other hand, the inter-observer can be overestimated, as there are studies reporting that the inter-observer variability was lower than 10%.

In practice, diagnosis of emphysema is based on a visual qualitative evaluation. CT criteria, such as the presence of low attenuation areas, pulmonary vascular interruption, and distortion, are used. Sakai et al. [14] defined the visual score method based on the severity and extent of the disease; they also found a correlation between visual scores and pulmonary function tests. The strongest correlation was found for FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC values. Similar correlations were reported in subsequent studies [16,17]. Some researchers determined the strongest correlation for DLCO values [18,19]. In our study, the strongest negative correlation values were obtained for DLCO, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC values, in that order.

Two alternative methods are used for a quantitative evaluation of density areas. One method directly measures density values, and the other calculates low attenuation areas with density values lower than a predefined value (i.e., a density mask) [20–22]. Regardless of the method, a strong correlation between RFTs and visual scores can be determined, which is confirmed by prior studies. We chose to directly measure lung parenchyma density. The main disadvantage of evaluating lung parenchyma quantitatively is that the time need for examination is much longer in comparison to the visual determination. An optimal determination must be quantitative, but it is problematic, especially in time-limited institutions.

When using quantitative methods, the density mask can be subjective; in this case, the extent of involvement is determined by the choice of a given cut-off value. Lower cut-off values tend to underestimate the disease severity, whereas higher cut-off value tend to overestimate it. On the other hand, the use of direct mean density values seems more objective, because it is independent from the cut-off value.

Because of these reasons, a direct measurement of density values was chosen in this study.

In the presence of airway obstruction, expiratory CT evaluation is based on the fact that some amount of air is trapped in the lungs. Lung density rises significantly on expiration, but in the case of airway obstruction, this effect is limited. There is a significant difference between inspiratory and expiratory density values, and this difference is negatively correlated with the severity of airway obstruction; this indicates that smaller amounts of air are moving on inspiration and expiration [23,24].

When the evaluation was performed on inspiration, the mean lung density values were within the 95% confidence interval in most patients, but this situation was reversed on expiration. Thus, expiration CT is more sensitive for evaluating airway obstruction. Our results were concordant with those found in the literature.

The main limitation of our study was a relatively low number of patients and controls, but this can be compensated by the clear results that were obtained. It is unlikely that

the results would be significantly different, if a larger sample had been used.

## Conclusions

Based on the results shown in Figure 1, DLCO is the best indicator of emphysematous parenchyma changes, and is closely followed by FEV<sub>1</sub> and FEV<sub>1</sub>/FVC. However, a strong correlation was not found with respect to other RFTs. As regards the comparison between the objective and subjective density values, HRCT visual density values are satisfactory. On the other hand, the best assessment can be performed with mean density values on expiration.

According to the results obtained in this study, RFTs other than FEV<sub>1</sub> and FEV<sub>1</sub>/FVC cannot be used as indicators of emphysematous parenchyma changes in COPD (namely, vital capacity (VC), total lung capacity (TLC), forced residual capacity (FRC) and residual volume (RV)).

## Conflict of interest

None.

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