Relationship between Lung Functions and Extent of Emphysema in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective: A study was undertaken to investigate whether the extent of emphysema, visually confirmed by high-resolution computed tomography (HRCT), in patients with COPD was associated with different indices of lung function and health-related life quality of patients with COPD.

Methods: Eighty-two patients with COPD underwent HRCT scanning; visual assessment of HRCT scan was used in the calculation of the assessment of the severity and extent of emphysematous destruction. The patients were clinically stable at the time of the evaluation. For all subjects, a detailed interview of disease history and symptoms, health-related quality of life (HRQL) measurement, and pulmonary function tests were performed.

Results: The mean visual emphysema score in all patients was 2.10±1.26. While the mean emphysema score in patients with COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 3 was 2.88±1.01, it was 1.54±1.13 in patients with COPD GOLD stage 2 (p<0.001). There was a significant correlation between the percentage of pulmonary emphysema and the numbers of pack-years smoked (r=0.58, p<0.001). The visual emphysema score was inversely correlated with FEV1 (r=-0.56, p<0.0001), FVC (r=-0.38, p<0.001), FEV1/FVC (r=-0.43, p<0.001), PEF (r=-0.44, p<0,001) and with carbon monoxide diffusion capacity (DLCO) (r=-0.50, p<0.001). There was no correlation between emphysema score and SGRQ.

Conclusion: These data suggest that HRCT visual scores correlate with functional indices of airflow obstruction and impaired lung diffusing capacity in patients with stable chronic obstructive pulmonary disease of varying severity, and the presence of pulmonary emphysema is best represented by FEV1 and DLCO.

Keywords: Chronic obstructive, computed tomography, emphysema, pulmonary disease

Özet

Amaç: Bu çalışmada kronik obstrüktif akciğer hastalarında (KOAH), görsel amfizem skoru ile değerlendirilen amfizemin yaygınlığı ile akciğer fonksiyonlarının değişik indeksleri ve hastaların hayat kaliteleri arasındaki ilişki araştırıldı.

Yöntemler: Seksen-iki KOAH hastasına yüksek rezolusyonlu bilgisayarlı tomografi (YRBT) çekildi, amfizemin ciddiyeti ve yaygınlığının hesaplanmasında görsel amfizem skoru kullanıldı. Tüm hastalar değerlendirme esnasında stabildi. Tüm hastaların ayrıntılı hikayeleri ve semptomları kaydedildi, sağlık ilişkili hayat kaliteleri ve solunum fonksiyon testleri ölçüldü.

Bulgular: Tüm hastaların görsel amfizem skoru ortalaması 2.10±1.26 idi. GOLD (Global Initiative for Chronic Obstructive Lung Disease) evre 3 olan hastalarda ortalama amfizem skoru 2.88±1.01 iken GOLD evre 2 hastalarında 1.54±1.13 idi (p<0.001). Pulmoner amfizem skoru ile sigara paket-yıl arasında anlamlı bir korelasyon vardı (r=0.58, p<0.001). Görsel amfizem skorunun, FEV1 (r=-0.56, p<0.0001), FVC (r=-0.38, p=0.001), FEV1/FVC (r=-0.43, p<0.001), PEF (r= -0.44, p<0,001) ve karbon monoksit difüzyon kapasitesi (DLCO) (r=-0.50, p<0.001) ile ters yönde korelasyonu vardı. Amfizem skoru ile SGRQ arasında bir korelasyon saptanmadı.

Sonuç: Bu veriler değişik şiddetteki stabil KOAH hastalarında, YRBT görsel amfizem skorunun hava yolu obstrüksiyonunun fonksiyonel indeksleri ve azalmış akciğer difüzyon kapasitesi ile arasında bir korelasyon olduğunu ve pulmoner amfizem varlığının en iyi FEV$_1$ and DLCO ile gösterildiğini ileri sürmektedir

Anahtar Kelimeler: Amfizem, bilgisayarli tomografi, kronik obtrüktif, pulmoner hastalik

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide and is projected to rank fifth in 2020 in burden of disease worldwide, according to a study published by the World Bank/World Health Organization (1). GOLD (Global Initiative for Chronic Obstructive Lung Disease) defines COPD as a disease state characterized by the presence of airway obstruction that is not fully reversible (1). In these patients, airflow obstruction is caused by the destruction of lung parenchyma (emphysema), airway narrowing, or both (2).

Pulmonary function testing offers a convenient tool for screening the disease earlier and assessing the progression of lung disease (3); however, the heterogeneity of disease can not be defined by FEV1 alone. The recently published guidelines of GOLD consider COPD patients as a homogeneous population, at least with regard to pharmacologic treatment (1). Accordingly, only simple spirometry is recommended to evaluate the presence and severity of airway obstruction. It is reasonable that a bet-

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ter understanding of the underlying disease may help to reduce the variability of response to therapeutic interventions in COPD patients.

High-resolution computed tomography (HRCT) scanning is considered to be a sensitive technique for detecting and quantifying pulmonary emphysema in vivo, but it may not be easy to obtain in many centers and is not suitable for follow-up (4). Studies attempting to relate pulmonary function measurements to HRCT scan yielded conflicting results, which makes it difficult to select the best functional indices that may indicate the degree of pulmonary emphysema, as evaluated by HRCT scan, the method of choice (5-7).

The aim of the present study was to examine how emphysema severity and extent affect a set of noninvasive pulmonary measures so that the extent of emphysema can be assessed by lung function tests and to determine which measurements are useful in achieving agreement with HRCT scan data in well-selected stable COPD patients with a wide range of bronchial obstructions.

METHODS

Subjects

This cross-sectional observational study recruited 82 patients (aged 63±7 years); body mass index (BMI): 26.9±5.4 kg/m^2 diagnosed with COPD consecutively from September 2008 to May 2011 in the pulmonary clinic at a university hospital. All patients had complete demographic data recorded, including age, duration of symptoms, and full smoking and medical history (Table 1).

A diagnosis of COPD was made according to the criteria of GOLD, as follows: COPD=presence of a post-bronchodilator FEV_1/FVC ratio <70% (1). The patients were clinically stable (no exacerbation for at least 2 months) at the time of the evaluation. All subjects were smokers or past smokers who had smoked ≥10 pack-years. Patients with a diagnosis of asthma, current active pulmonary tuberculosis, or any other clinically relevant lung disease (bronchiectasis, pleural effusion, any history of lung cancer, lung resection, cystic fibrosis, allergic alveolitis, or pulmonary fibrosis) and patients with bronchodilator reversibility were excluded. All patients provided written informed consent and approved by the ethical committee at the Ondokuz Mayıs University Hospital (ethical committee number=2010-144).

Pulmonary Function Tests

Pulmonary function tests (PFTs) were performed with a ZAN system (ZAN^{100}; ZAN Gerätetechnik GmbH, Oberthulba, Germany). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak expiratory flow rate (PEFR), and reversibility testing with 400 µg inhaled salmeterol were performed according to the American Thoracic Society/European Respiratory Society consensus guidelines (8). Carbon monoxide diffusing capacity (DL_{CO}) was performed with an EasyOne Pro (EasyOne Pro; Andover, Massachusetts, USA). DL_{CO} using the single-breath method was measured as described by Huang and Macintyre (9). FVC, FEV_1, PEFR, and DL_{CO} were expressed as percentage of predicted values (8).

CT Scans and Reading of Images

Low-attenuation areas (LAAs) were quantified by HRCT scan. CT scans were performed in a supine position using spiral CT scanners (Discovery CT750HD; GE Healthcare, Milwaukee, WI, USA or Somatom; Siemens Healthcare, Erlangen, Germany). No contrast media was

used. CT scans were obtained after deep inspiration. This minimized the influence of variable hyperinflation, allowed us to compare the results under the same conditions, and optimized breath-holding time. An experienced chest radiologist made the interpretation, unaware of the clinical and lung function data. The reader viewed the images on a high-resolution monitor in its typical window and level settings with maximum magnification while scrolling through the images one by one. Interpretations were performed using standard lung settings (collimation, 1.5 mm; width, 1500 Hounsfield units; level, -650 Hounsfield units).

Visual Emphysema Score

Emphysema was identified as areas of hypovascular low attenuation. On three HRCT slices (at the level of the carina and 5 cm above and 5 cm below the carina), the lung parenchyma was assessed for extent of emphysema. The three levels were graded and scored separately for the left and right lung, giving a total of six lung fields. Emphysema distribution was graded with a 5-point scale based on the percentage of lung involved: 0, no emphysema; 1, up to 25% of lung parenchyma involved; 2, between 26% and 50% of lung parenchyma involved; 3, between 51% and 75% of lung parenchyma involved; and 4, between 76% and 100% of lung parenchyma involved.

St George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) was used to assess health-related quality of life. This is a supervised self-administered measure, designed specifically for use in respiratory disease, and contains three domains: symptoms (relating to cough, sputum, wheeze, and shortness of breath); activity (relating to physical activity limited by breathlessness); and impact (relating to control, panic, medication, and expectations) (10). A total score was calculated from all three domains.

Statistical Analysis

The normality of the data distribution was assessed by the Shapiro-Wilks test. Pearson's correlation coefficient was used to determine relationships between normally distributed or log-transformed variables; otherwise, Spearman's rank test was used. Independent-sample t-tests were utilized in comparing means between groups with dichotomous data. Two-sided p values <0.05 were considered statistically significant. Data were analyzed using SPSS statistical software (Mac version 21.00, serial number; 10229569, SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 167 patients with COPD from a university hospital were recruited. We were able to perform clinical and radiological evaluations for 128 patients. Of these, 46 were not included in the study, because they had clinically relevant pulmonary problems. Thus, the final population had 82 male patients, whose clinical and demographic data are shown in Table 1. The flow chart for the selection of the participating patients is shown at Figure 1.

Of these 82 patients, 48 patients had moderate obstruction (GOLD stage 2), and 34 patients had severe obstruction (GOLD stage 3). Table 1 shows the patients' pulmonary function characteristics.

The mean visual emphysema score in all patients was 2.10±1.26. The mean visual emphysema score was higher in patients with COPD GOLD stage 3 than in patients with GOLD stage 2: 2.88±1.01 vs.

Figure 1. Flow chart for the selection of the participating patients

Figure 2. Percentage of patients according to visual emphysema score
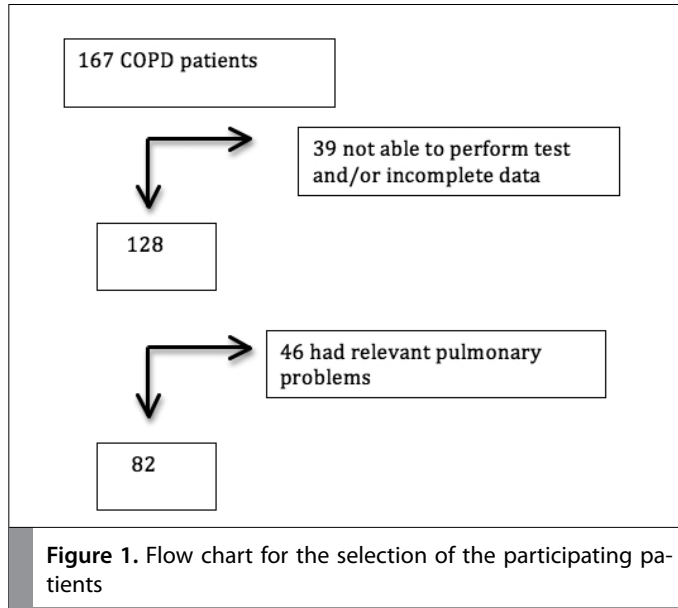
1.54±1.13, respectively (p<0.001). The majority of stage 3 patients had visual emphysema score 3, whereas stage 2 patients had visual emphysema score 1. The percentage of patients according to visual emphysema score is shown in Figure 2.

The BMI was lower in patients with GOLD stage 3 than GOLD stage 2: 28.7±5.3 kg/ m² versus 24.4±4.5 kg/ m², respectively (P<0.0001) (Table 2).

There was a significant correlation between the percentage of pulmonary emphysema and the numbers of pack-years smoked (r=0.58, p<0.001). The visual emphysema score was inversely correlated with FEV_1 (r=-0.56, p<0.0001), FVC (r=-0.38, p=0.001), FEV_1/FVC (r=-0.43, p<0.001), PEF (r=-0.44, p<0.001), and DL_{CO} (r=-0.50, p<0.001) (Table 3).

No correlation was found between the emphysema score and FEV1% change and SGRQ. The relationships of emphysema score with lung function parameters and arterial blood gases are reported in Table 3.

DISCUSSION

The main finding of the present study is that an increase in visual emphysema score, evaluated by thorax HRCT, results in decreased lung functions, airflow obstruction, and decreased carbon monoxide diffusion test, and of these parameters, presence and severity of emphysema correlate best with FEV1 and impaired gas exchange capability in patients with different severities of COPD, based on GOLD criteria.

Chronic obstructive pulmonary disease is a very inhomogeneous condition, and a better characterization of the phenotype of the disease may help to reduce the variability of response to therapeutic interventions in COPD patients (11). Spirometry is widely used to evaluate the presence and severity of airway obstruction, while the assessment of emphysema by HCRT scan is restricted to those patients who are possible candidates for surgery (12). In the last few years, great attention has been paid to drugs that specifically address either airflow obstruction (e.g., phosphodiesterase inhibitors) or parenchymal damage (e.g., $α_1$-antitrypsin augmentation therapy). From this perspective, the variability of response to treatments could be reduced by assessing patients for the presence and extent of emphysema (12).
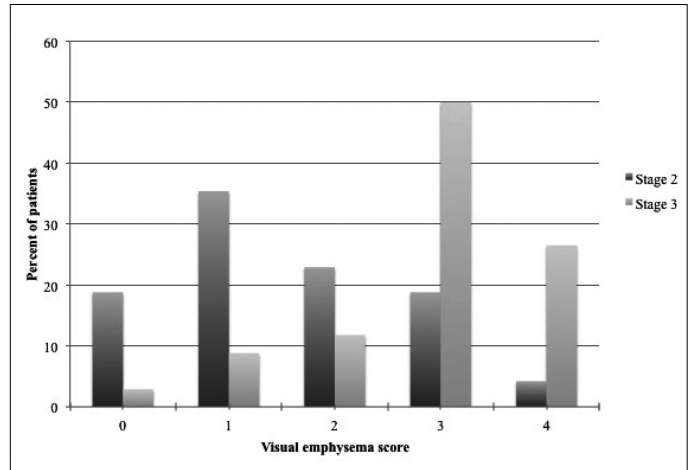
Table 1. Demographic, clinical, and physiologic characteristics of the patients

Characteristics	Mean±SD
Age, year	63±7
Body mass index, kg/m²	26.9±5.4
COPD duration, year	5.6±2.7
Smoking, pack-years	55.0±8.3
*FEV_1 change, % predicted	2.4±1.9
FEV_1, % predicted	53.1±12.0
FVC, % predicted	70.6±13.1
FEV1/FVC (%)	55.0±9.2
PEF %	51.6±16.1
FEF25-75 %	23.1±7.9
DL_{CO}, % predicted	56.3±17.1
Total SGRQ	54.4±12.9

*Reversibility testing with 400 µg inhaled salmeterol.

COPD: chronic obstructive pulmonary disease; DLCO: carbon monoxide diffusing capacity; FEV_1: forced expiratory volume in 1 second; FEF: forced expiratory flow; FVC: forced vital capacity; PEF: peak expiratory flow; SGRQ: St. George's respiratory questionnaire

Table 2. GOLD stages of COPD and visual emphysema score

COPD GOLD Stage (Number of patients)	Stage 2 (n: 48)	Stage 3 (n: 34)	p value
Body mass index, ±SD, (kg/m²)	28.7±5.3	24.4±4.5	<0.0001
Mean visual emphysema score±SD	1.54 ±1.13	2.88 ±1.01	<0.0001

Evaluation of emphysema by HRCT is a noninvasive method that best assesses the severity, extent, and progression of emphysema in clinical practice; however, the use of HRCT scanning for the assessment of emphysema has some limitations. First, it may not be easy to obtain in a number of centers. Second, it exposes the patient to radiation. Third, it can not be taken as an indisputable "gold standard" for the

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quantification of emphysema, as it provides correlation coefficients, with lung pathology ranging from 0.7 to 0.9 (13). However, lung function tests are easy to obtain in most centers, but the relationships between single parameters and the extent of emphysema, determined either by pathology or HRCT scan, are rather weak. The present study gives an answer to the two following practical questions: first, how the severity and extent of emphysema affect a set of noninvasive pulmonary measures, and secondly, whether the extent of emphysema can be assessed by lung function tests and which measurements are useful in achieving agreement with HRCT scan data.

We used a subjective method for the estimation of emphysema-i.e., visual score (14). It has been reported that the analysis of visual scoring may lead to a systematic overestimation of emphysema (15). However, the majority of studies has shown reasonably good correlations between CT emphysema scores and the pathological specimen, a good agreement between expert readers for the assessment of the presence and extent of emphysema, and good correlations between subjective and objective assessments of emphysema (7). Our finding is in agreement with previous studies in which the visual emphysema score is inversely correlated with FEV1, FVC, FEV1/FVC, PEF, and DL_{CO} (7, 12). Visual emphysema score correlated inversely best with FEV1 and DL_{CO} in our study; however, it correlated inversely best with FEV_1/FVC and DL_{CO} in a previous study (7).

In our study, there was also an inverse relationship between visual emphysema score and DL_{CO}. Diffusion capacity is reduced in emphysema patients because of the loss of alveolar-to-capillary surface, but it also may be decreased due to very severe airway obstruction.

Our data suggest that the presence of pulmonary emphysema is best represented by FEV_1 and the impaired gas exchange capability of the respiratory system in patients with stable chronic obstructive pulmonary disease of varying severity.

We observed a statistically significant correlation between HRCT-scored emphysema and number of pack-years smoked. These findings are in agreement with a study by Patel and colleagues (16), who found a significant relationship between pack-years smoked and emphysema in a large group of COPD patients.

In our study, there was no correlation between emphysema score and quality of life measured by the SGRQ, because the presence of emphysema had less impact on the clinical presentation of patients in our group. This is an important finding, which is in accordance with previous reports (17). It has been estimated that 30% of the lung must be destroyed by emphysema before symptoms become evident (18). It is possible that with such small degrees of emphysema, mechanisms other than changes in elastic recoil may be responsible for the physiologic impairment.

Mair et al. (19) analyzed variables that might predict the severity of emphysema and found that BMI was the best predictor. In our study group, we found a strong inverse correlation between BMI and the extent of emphysema, which correlates with the knowledge that BMI is tightly associated with emphysema, at least in patients with normal BMI and diffuse emphysema.

As a result, it may be argued that the knowledge of the presence of emphysema is not important. One could postulate that knowing whether emphysema exists in patients with moderate or severe

COPD adds little to the clinical management. However, FEV_1 correlates weakly with clinical outcomes and health status in patients with COPD (20). Moreover, because FEV_1 is a global measurement of lung function, it can not capture the heterogeneity of COPD or its many different clinical phenotypes. The advent of novel pulmonary imaging methods that can be rapidly and safely deployed has enabled COPD research to move beyond FEV_1 by facilitating and amplifying clinical phenotyping measurements, providing quantitative information, and detecting significant responses to therapy, even in the absence of significant FEV_1 improvements. For example, until recently, it was unclear why patients with COPD using inhaled bronchodilators experienced significant symptomatic improvements despite very modest improvements in FEV_1. Now, the picture is clearer, because pulmonary imaging techniques provide a way to visualize and quantify regional improvements in ventilation over time and in response to bronchodilator therapy, even in the absence of clinically relevant changes in FEV_1 (21). Furthermore, the presence of emphysema significantly increases the risk of lung cancer in these patients (22). For this reason alone, we believe that identifying emphysema in patients with COPD is important for their long-term care.

Study Limitations
The small sample size is a limitation of this study. The lack of women is also important, as it is now well known that there are important sex differences in the severity and distribution of emphysema. Women have less severe emphysema than men, and it is generally centrally distributed, with smaller areas of low attenuation (18). This limitation precludes an assessment of the role that the presence, severity, and distribution of emphysema might have on the clinical presentation of the disease in women. Knowing that there are consistent sex differences in the clinical presentation of the disease, we believe it is important to further investigate this issue with an appropriate cohort. Finally, because our study population was limited to patients with moderate to severe COPD, these findings can not be extrapolated to patients with preserved lung function and emphysema.

CONCLUSION
In conclusion, in this group of patients with moderate to severe COPD, the presence of emphysema, regardless of its distribution, has an impact on physiologic parameters but not on the clinical presentation of the disease. As documented in the present study, lung function tests have some limitations as regards the measurements of airway obstruction and lung dysfunction, particularly in patients with predominant pulmonary emphysema; however, the use of well-selected and appropriate lung function measurements may be helpful in giving an estimate of the extent of emphysema in the follow-up monitoring of patients with COPD. Further studies should confirm the importance of our findings.

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