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

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Abstract

Background: To investigate whether the extent of emphysema, visually confirmed by high resolution computed tomography (HRCT) in patients with COPD were associated with different indices of lung functions.

Methods: Eighty-two patients with COPD underwent HRCT scanning; visual assessment of HRCT scan was used in the calculation of extent of emphysematous

Destruction: The patients were clinically stable at the time of the evaluation. All subjects were smokers or past smokers who had smoked>10 pack-years.

Results: The mean visual emphysema score in all patients was 2.21 ± 1.11. While the mean emphysema score in patients with COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 3 was 2.88 ± 1.03, it was 1.54 ± 1.16 in COPD GOLD stage 2 ($p<0.001$). There was a significant correlation between the emphysema score and the numbers of pack/years smoked ($R=0.58$, $p<0.001$). The visual emphysema score was inversely correlated with the 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 the Carbon monoxide diffusing capacity divided by the alveolar volume (DLCO/VA) ($r=-0.50$, $p<0.001$). In our study population, patients had a limited expression of the disease as represented by low scores in Saint George Respiratory Questionnaire (SGRQ), and there was no correlation between emphysema score and SGRQ.

Conclusions: HRCT visual scores correlated with functional indices of airflow obstruction and impaired lung diffusing capacity in patients with stable COPD of varying severity, the presence of pulmonary emphysemais best represented by the FEV1 and DLCO/VA.

Keywords: Emphysema; Pulmonary disease; Chronic obstructive; Computed tomography

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 destruction of lung parenchyma (emphysema), airway narrowing, or both [2].

Pulmonary function testing offers a convenient tool for earlier screening of disease, and assessing progression of lung disease [3], however the heterogeneity of disease cannot be defined by the 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 better 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 make 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 whether the extent of emphysema can be assessed by lung function tests; and which measurements are useful in achieving agreement with HRCT scan data in well-selected stable COPD patients with a wide range of bronchial obstruction

Material and Methods

Subjects

This cross-sectional observational study recruited 82 patients (aged 63 ± 8 years; body mass index (BMI): 22.3 ± 3.5 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).

Variables	Mean (Sd)	Range
Age, year	63 (8)	46-79
Body mass index, kg/m^2	22.3 (3.5)	15-40
COPD duration, year	5.6 (2.69)	1-10
Smoking, packet/year	55 (8.3)	25-100
*FEV1 change, % predicted	2,4 (1.87)	0,20-6,90
FEV, % predicted	53.1 (12)	31-74.30
FVC, % predicted	70.6 (13)	38,30-98,00
FEV1/FVC	55.5 (8.6)	29,80-70,60
PEF %	51.6 (16)	17,10-79,50
FEF25-75 %	23.1 (7.9)	9,6-43,9
DLCO/VA, % predicted	56.3 (17)	28-78
Total SGRQ	54.4 (12,9)	21-73

Table 1: Demographic, Clinical and the Physiologic Characteristics of Patients

*Reversibility testing with 400 μg inhaled salmeterol, COPD: Chronic Obstructive Pulmonary Disease, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow, FEF: Forced Expiratory Flow, DLCO/VA: The Carbon monoxide diffusing capacity divided by the alveolar volume, SGRQ; St. George's Respiratory Questionnaire

A diagnosis of COPD was made according to the criteria of GOLD, as follows: COPD=presence of a post-bronchodilator FEV1/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 and patients with bronchodilator reversibility were excluded. All patients provided written informed consent approved by the ethical committee at the Ondokuz mayis University Hospital (ethical committee number=2010-144).

Pulmonary function test

Pulmonary Function Tests (PFT) were performed with a ZAN system (ZAN100; ZAN Gerätetechnik GmbH, Oberthulba, Germany). Forced Vital Capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), reversibility testing with 400 μg inhaled salmeterol were performed according to the American Thoracic Society/European Respiratory Society consensus guidelines [8]. The Carbon monoxide diffusing capacity divided by the alveolar volume (DLCO/VA) was performed with Easy One Pro (Easy One Pro; Andover, Massachusetts, USA). DLCO/VA using the single-breath method was measured as described by Huang and Macintyre [9]. FVC, FEV1, PEFR and DLCO/VA were expressed as percentage of predicted values [8].

CT scans and reading of images

Low Attenuation Areas (LAA) was quantified by HRCT scan. CT scans were performed in a supine position using the 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 interpretation, unaware of the clinical and lung function data. The reader viewed the images on a high-resolution monitor at 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, 1.500 Hounsfield units; level, -950 Hounsfield units).

Visual emphysema score

Emphysema was identified as areas of hypovascular low attenuation. The HRCT quantification was calculated by visual emphysema score described by Sakai et al (sakai score) [10]. In this method; Emphysema distribution was graded with a five-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) [11]. 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 evaluation of 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 (Figure 1), whose clinical and demographic data are shown in table 1.

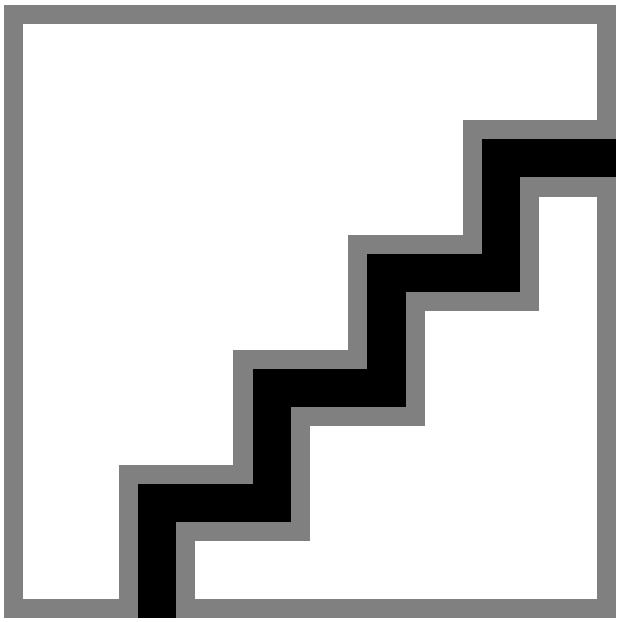

Figure 1: Flow chart for the selection of the participating patients

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 2.21 ± 1.11. While the mean emphysema score was higher in patients with COPD GOLD stage 3 than patients with GOLD stage 2; 2.88 ± 1.03 vs. 1.54 ± 1.16 respectively (p<0.001).

The BMI was lower in patients with GOLD stage 3 than GOLD stage 2; 28.67 ± 5.34 kg/m^2 vs. 24.41 ± 4.55 kg/m2 respectively (P<0.0001) (Table 2).

COPD GOLD Stage (number of patients)	Stage 2 (n: 48)	Stage 3 (n: 34)	P value
Mean visual emphysema score	1.5 (1.2)	2,9 (1.1)	P<0.0001
Body mass index, kg/m^2	28.7 (5.3)	24.4(4.6)	P<0.0001

Table 2: GOLD stages of COPD and visual emphysema score

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 the 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 DLCO/VA (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, arterial blood gases were reported in table 3.

Visual emphysema score	r value	p value
FEV1%	-0,560	P<0,0001
FVC%	-0,376	P<0,001
FEV1/FVC	-0,426	P<0,0001
PEF%	-0,439	P<0,0001
FEF 25-75%	-0,421	P<0,0001
*FEV1 change, % predicted	-0,125	0,265
DLCO/VA	-0,497	P<0,001
pH	-0,135	P=0,228
PaO_2 (mmHg)	-0,398	P<0,0001
$PaCO_2$ (mmHg)	0,360	0,001
Sat O_2 (%)	-0,355	0,001
Total SGRQ	0,118	0,257
Smoking pack/ years	0.586	P<0,0001

Table 3: Relationship Between Functional Variables and Emphysema Extent as Assessed by HRCT Scan

*Reversibility testing with 400 μg inhaled salmeterol, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow, FEF: Forced Expiratory Flow, DLCO/VA: The Carbon monoxide diffusing capacity divided by alveolar volume, Sat O2: Oxygen saturation, SGRQ; St. George's Respiratory Questionnaire

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, emphysema presence and severity is best correlated with FEV1 and impaired gas exchange capability in patients with different severities of COPD based on GOLD criteria.

Chronic obstructive pulmonary disease is very inhomogeneous condition and a better characterization of the phenotype of disease may help to reduce the variability of response to therapeutic interventions in COPD patients [12]. 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 [13]. In the last few years, great attention has been paid to drugs that specifically address either airflow obstruction (e.g., phosphodiesterases inibitors) or parenchymal damage (e.g., α1-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 [13].

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 cannot be taken as an indisputable "gold standard" for the quantification of emphysema, as it provides correlation coefficients with lung pathology ranging from 0.7 to 0.9 [14]. 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 following two practical questions: first, how emphysema severity and extent affect a set of noninvasive pulmonary measures, 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 [15]. It has been reported that the analysis of visual scoring may lead to a systematic overestimation of emphysema [16]. However, the majority of studies have shown reasonably good correlations between CT emphysema scores and 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 assessment of emphysema [7].

Our finding is in agreement with previous studies [7,13] that the visual emphysema score was inversely correlated with the FEV1, FVC, FEV1/FVC and PEF.

In our study there was also an inverse relationship between visual emphysema score and DLCO/VA. The DLCO/VA 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 the FEV1 and 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 [17] that 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. It is because; the presence of emphysema has less impact on the clinical presentation of in this patient's population. This is an important finding which is in accordance with previous reports [18]. It has been estimated that 30% of the lung must be destroyed by emphysema before symptoms become evident [19]. 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. [20] analyzed variables that might predict the severity of emphysema and found that BMI was the best predictor. In our patient population, we found a strong inverse correlation between BMI and extend of emphysema that is in correlation 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 emphysema's presence is not important. Based on the current study, one could postulate that knowing emphysema in patients with moderate or severe COPD adds little to clinical management. However, we do not know what impact mild degrees of emphysema might have on the natural course of the disease. Furthermore, the presence of emphysema significantly increases the risk of lung cancer in these patients [21]. 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 emphysema severity and distribution. Women have less severe emphysema than men, and it is generally centrally distributed with smaller areas of low attenuation [19]. 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 is limited to patients with moderate to severe COPD, these findings cannot be extrapolated either to patients with preserved lung function and emphysema.

Conclusion

In conclusion, in this patient population 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 to give 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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