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High-Resolution Computed Tomography Quantitation of Emphysema Is Correlated with Selected Lung Function Values in Stable COPD

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Key Words
Emphysema · Chronic obstructive pulmonary disease · High-resolution computed tomography · Lung structural alterations

Abstract
Background: The literature shows conflicting results when high-resolution computed tomography (HRCT) scores of emphysema were correlated with different indices of airflow obstruction. ***Objectives:*** We correlated HRCT scores of emphysema with different indices of airflow obstruction. ***Methods:*** We performed HRCT of the chest in 59 patients, all smokers or ex-smokers, with stable chronic obstructive pulmonary disease of different severity [GOLD stages I–IV; mean age ± SD 67.8 ± 7.3 years; pack/years 51.0 ± 34.6; percent predicted forced expiratory volume in 1 s (FEV_1% predicted) 52.3 ± 17.6; post-bronchodilator FEV_1% predicted 56.5 ± 19.1; FEV_1/forced vital capacity (FVC) ratio 50.8 ± 10.2; post-bronchodilator FEV_1/FVC ratio 51.6 ± 11.0; percent diffusion lung capacity for carbon monoxide (DLCO%) 59.2 ± 21.1; DLCO/percent alveolar volume (VA%) 54.5 ± 18.2; percent residual volume 163.0 ± 35.6; percent total lung capacity (TLC%) 113.2 ± 15; residual volume/TLC 1.44 ± 0.2]. All patients were in stable phase. ***Results:*** The mean ± SD visual emphysema score in all patients was 25.6 ± 25.4%. There was a weak but significant correlation between the percentage of pulmonary emphysema and numbers of pack/years ($R = +0.31$, $p = 0.024$). The percentage of emphysema was inversely correlated with the FEV_1/FVC ratio before and after bronchodilator use ($R = -0.44$, $p = 0.002$, and $R = -0.39$, $p = 0.005$), DLCO% ($R = -0.64$, $p = 0.0003$) and DLCO/VA% ($R = -0.68$, $p < 0.0001$). A weak positive correlation was also found with TLC% ($R = +0.28$, $p = 0.048$). When patients with documented emphysema were considered separately, the best significant correlation observed was between DLCO/VA% and HRCT scan score ($p = 0.007$). ***Conclusions:*** These data suggest that in patients with stable chronic obstructive pulmonary disease of varying severity, the presence of pulmonary emphysema is best represented by the impaired gas exchange capability of the respiratory system.

Introduction

Chronic obstructive pulmonary disease (COPD) is an illness characterized by progressive chronic airflow limitation, not fully reversible [1]. This airflow limitation is usually progressive and associated with an abnor-

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Table 1. Patient characteristics (n = 59)

Characteristic	Mean ± SD
Age, years	67.88 ± 7.34
Pack/years	51.03 ± 34.61
Pre-bronchodilator FEV_1%	52.31 ± 17.69
Post-bronchodilator FEV_1%	56.55 ± 19.11
Pre-bronchodilator FEV_1/FVC%	50.82 ± 10.25
Post-bronchodilator FEV_1/FVC%	51.61 ± 11.07
Pre-bronchodilator FVC%	80.51 ± 20.06
Post-bronchodilator FVC%	85.09 ± 19.98
DLCO%	59.23 ± 21.15
DLCO/VA%	54.54 ± 18.22
Pa_{O_2}, mm Hg	68.03 ± 12.04
Pa_{CO_2}, mm Hg	42.17 ± 8.34
pH	7.42 ± 0.02
RV%	163.03 ± 35.64
TLC%	113.2 ± 15.46
RV/TLC%	1.44 ± 0.21
Emphysema, %	25.62 ± 25.39

mal inflammatory response of the lung to noxious particles.

Pathological changes characteristic of COPD are found in the central and peripheral airways, lung parenchyma and pulmonary vasculature [2, 3]. Chronic airflow limitation is attributed to the narrowing of the small airway lumen due to morphological changes and a decrease in lung elastic recoil due to parenchyma destruction. Emphysema is a pathological diagnosis defined by permanent enlargement of airspaces distal to the terminal bronchioles accompanied by the destruction of alveolar walls and without obvious fibrosis. High-resolution computed tomography (HRCT) has a good correlation with the pathologic evaluation of emphysema ex vivo ($R > 0.9$) and in vivo ($R = 0.7–0.9$) [4, 5].

HRCT can be considered a sensitive technique for detecting and quantifying pulmonary emphysema in clinical practice [6]. There is a correlation between the pathologic grade of emphysema on resected lung specimens and the preoperative CT score [7]. A CT scan has been shown to be useful to assess the presence, extent and types of emphysema. Quantitative CT has already been used in patient selection for surgical treatment of pulmonary emphysema and in pharmacological trials [1, 8, 9]. However, the use of HRCT to assess pulmonary emphysema in COPD has some limitations, e.g., lack of reproducibility, disagreements on the best method to analyze the lung parenchyma, patients' radiation exposure and the difficulty to obtain it in some centers, making this technique not suitable for follow-up [8]. Moreover, longitudinal studies with an adequate sample size are lacking [10–12]. Noninvasive pulmonary measurement is easy to obtain, standardized, safe for the patient, reproducible and suitable for follow-up but it is less sensitive than HRCT in detecting disease progression [13, 14]. Correlation studies between HRCT evaluation of emphysema and specific measures of pulmonary function have yielded conflicting results [6, 15–17]. A correlation has been reported between the HRCT-evaluated extent of emphysema and forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), functional residual capacity, residual volume (RV), diffusion lung capacity for carbon monoxide (DLCO), DLCO/alveolar volume (VA) ratio and bronchodilator-induced change in FEV_1/forced vital capacity (FVC) ratio. However, the presence and extent of these correlations is conflicting across different studies [6, 15–17], making it difficult to select the best functional indices which may indicate the degree of pulmonary emphysema, as evaluated by HRCT scan, the method of choice. The aim of the present study was to examine the capability of a set of noninvasive pulmonary measures to assess the severity of emphysema in well-selected stable COPD patients, with a wide range of bronchial obstruction, by performing a multivariate analysis between HRCT-evaluated emphysema and these pulmonary function measures.

Subjects and Methods

Subjects

In this study, we enrolled 59 subjects (53 males and 6 females) affected by COPD [1]. Table 1 shows the patients' demographic characteristics. The severity of the airflow obstruction was staged using current GOLD criteria [1]. COPD was defined according to international guidelines, as follows: COPD = presence of a post-bronchodilator FEV_1/FVC ratio <70% [1]. All patients were current or former smokers. All were in a stable clinical condition and had not experienced respiratory exacerbations in the previous 4 weeks. None of the subjects were treated with theophylline, antibiotics, antioxidants, mucolytics and/or glucocorticoids in the month prior to the execution of pulmonary function tests. Only bronchodilator use was allowed up to 24 h before performance of the pulmonary function tests. The study was approved by the local ethical committee and informed consent was obtained from all subjects.

Pulmonary Function

A complete lung function test was carried out before and 30 min after inhalation of 200 μg of salbutamol using the Vmax 22 system (Sensor Medics Corporation, Yorba Lynda, Calif., USA). At baseline and after salbutamol administration, FVC and FEV_1 were measured according to the American Thoracic Society

guidelines [18]. Thoracic gas volume (TGV) was measured by body plethysmography, with the subjects panting against a closed shutter at a frequency slightly <1 Hz with their cheeks supported by their hands. TLC was obtained as the sum of TGV and linked inspiratory capacity. RV was the difference between TLC and a relaxed vital capacity. Functional residual capacity was obtained from TGV values that were corrected for any difference between the volume at which the shutter was closed and the average end-expiratory volume of the four preceding regular tidal breaths. Predicted values for spirometry and lung volumes were measured according to Quanjer et al. [19]. DLCO and VA were measured at least in duplicate, as described by Huang and Macintyre [20]. Predicted values were derived from Cotes et al. [21].

HRCT Imaging

Chest HRCT scans were performed in the supine position with the breath held at full inspiration. HRCT images were selected at three levels including the aortic arch, carina and 1–2 cm above the highest hemidiaphragm.

A General Electric Lightspeed 16 Plus CT scanner was used. The quantitative evaluation of emphysema was obtained by visual score technique [22] modified by Zompatori et al. [23]. The CT scan was performed using 140 kV, 200 mA, 1 s scanning time and 1.25 thickness, a window level between –500 and –700 Hounsfield unit, and a window width between 1,000 and 2,000 Hounsfield unit. Emphysema was identified as areas of hypovascular low attenuation and was also 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 = 26–50%, 3 = 51–75%, and 4 = 76–100% of lung parenchyma involved [24].

Data Analysis

Group data were expressed as the mean ± standard deviation for functional data. Correlation coefficients were calculated using the Spearman rank method. Multiple regression analysis was performed for selected functional parameters which presented the best R and p values at the preliminary determination by the Spearman rank method. Probability values of $p \leq 0.05$ were considered significant. Data analysis was performed using the StatView SE Graphics program (Abacus Concepts Inc., Berkeley, Calif., USA).

Results

All 59 subjects were smokers or former smokers (mean pack/years 51 ± 34). The mean age was 67.88 ± 7.36 years. All patients were in stable clinical conditions, as assessed by an arterial pH >7.35. Twenty-four patients had severe or very severe obstruction (GOLD III–IV) and 35 patients had a mild-to-moderate obstruction (GOLD I–II) not reversible after administration of salbutamol (table 1). Table 1 shows the patients' lung function characteristics. The mean extent of emphysema determined by HRCT scan was 25.65 ± 25.39%. Statistically significant correlations were observed between percentage of emphysema and pack/years (R = 0.31, p = 0.02; fig. 1a), TLC (R = 0.28, p = 0.048; fig. 1b), pre-bronchodilator FEV_1/FVC% (R = –0.44, p = 0.002; fig. 1c), post-bronchodilator FEV_1/FVC% (R = –0.39, p = 0.005; fig. 1d), DLCO% (R = –0.64, p = 0.0003; fig. 1e), and DLCO/VA (R = –0.68, $p < 0.0001$; fig. 1f). When the percentage of emphysema was considered as a dependent variable, multivariate analysis showed a significant inter-relationship with pre-bronchodilator FEV_1/FVC% and DLCO/VA%, considered as independent variables (p = 0.011 and $p < 0.0001$, respectively; fig. 2). No correlation was found between the GOLD stages of COPD and the severity of emphysema. In all patients, our quantitative visual score of emphysema was highly and significantly correlated with the NETT Research Group subjective visual grading score [24] (R = 0.962, $p < 0.0001$). When the analysis was restricted to the 33 patients with documented emphysema (>10% HRCT scan score), DLCO/VA% was the functional parameter, of those we studied, most significantly associated with the percentage of emphysema (R = –0.576, p = 0.010; fig. 3a). A weaker correlation was observed between the percentage of emphysema and DLCO% (R = –0.541, p = 0.016). Multiple regression analysis, performed with the two most sensitive parameters, pre-bronchodilator FEV_1/FVC% and DLCO/VA%, confirmed the association between DLCO/VA% and the scored emphysema as the most significant (R = 0.632, intercept, p = 0.0001; pre-bronchodilator FEV_1/FVC%, p = 0.275; DLCO/VA%, p = 0.007; fig. 3b). A weaker correlation was observed between DLCO% and the scored emphysema (R = 0.620, intercept, p = 0.0001; pre-bronchodilator FEV_1/FVC%, p = 0.135; DLCO%, p = 0.011).

Discussion

In this study, HRCT-evaluated emphysema correlated at univariate analysis with the numbers of pack/years, TLC, pre- and post-bronchodilator FEV_1/FVC values, DLCO and DLCO/VA, and at multivariate analysis with pre-bronchodilator FEV_1/FVC, DLCO and DLCO/VA. We developed a multivariate analysis including the percentage of emphysema as dependent variable, and pre-bronchodilator FEV_1/FVC%, DLCO% and DLCO/VA% measures as independent variables, since these parameters of respiratory function are easy to obtain, safe, standardized and suitable for follow-up monitoring of COPD patients. The two dependent variables, FEV_1/FVC% and DLCO/VA%, were the best functional parameters associated to the variations of percentage of emphysema, as evaluated by the preliminary single regression analysis (fig. 1). In

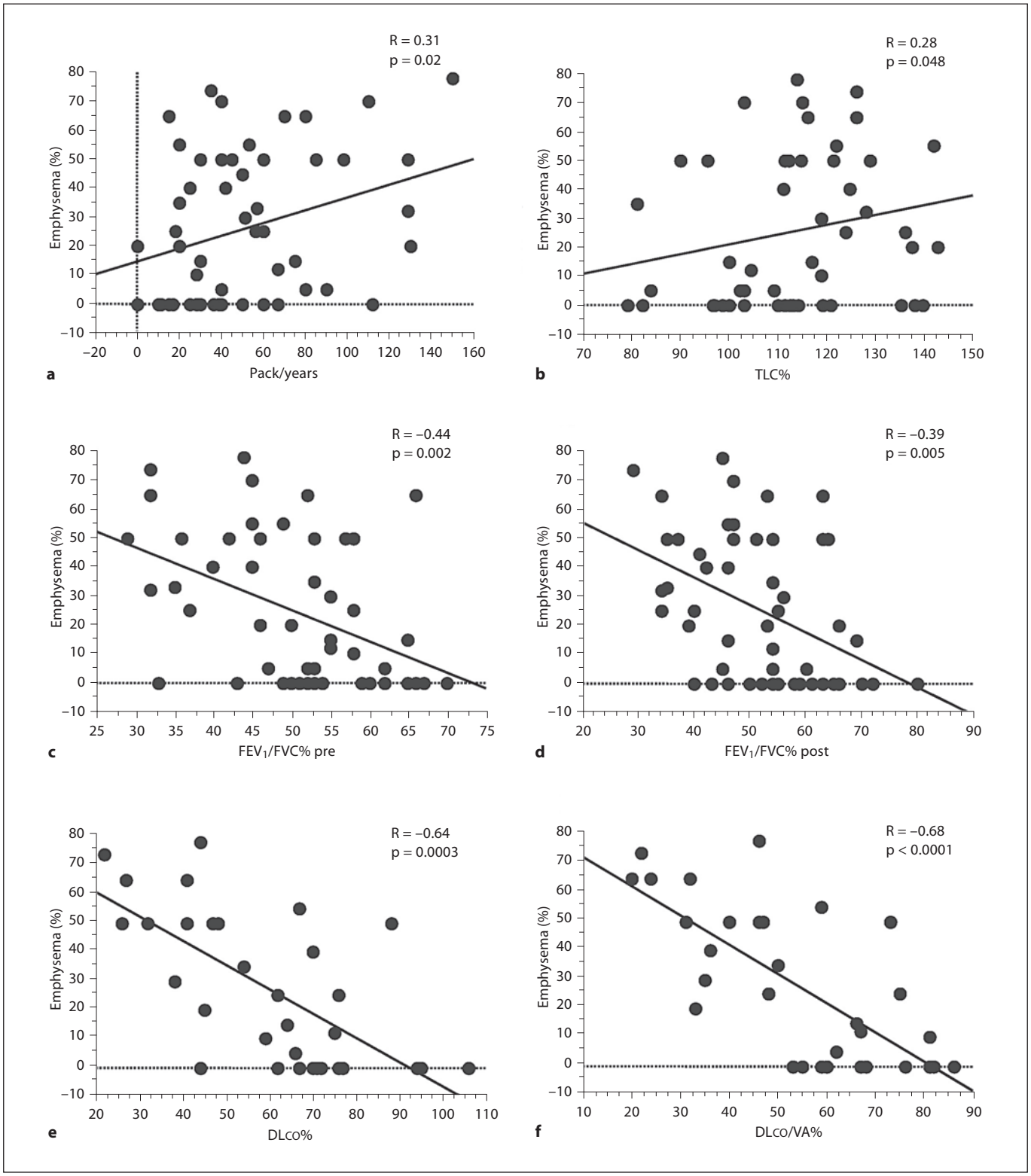

Fig. 1. Regression analysis showing a significant positive correlation between the percentage of emphysema, evaluated by HRCT scan score, and the number of pack/years smoked (**a**) and TLC (**b**). A negative significant association was observed between the percentage of emphysema and pre-bronchodilator (pre) $FEV_1/FVC\%$ (**c**), post-bronchodilator (post) $FEV_1/FVC\%$ (**d**), DLCO% values (**e**), and DLCO/VA% values (**f**).

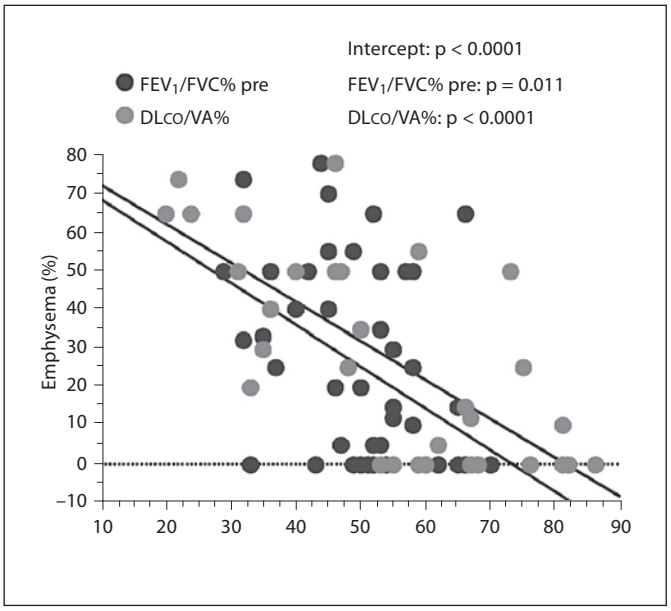

Fig. 2. Multiple regression analysis, performed in all COPD patients, considering FEV_1/FVC% and DLCO/VA% as independent variables and the degree of emphysema as dependent variable. This multiple regression shows a significant association of both pre-bronchodilator (pre) FEV_1/FVC% and DLCO/VA% with the degree of emphysema, as measured by HRCT scan score.

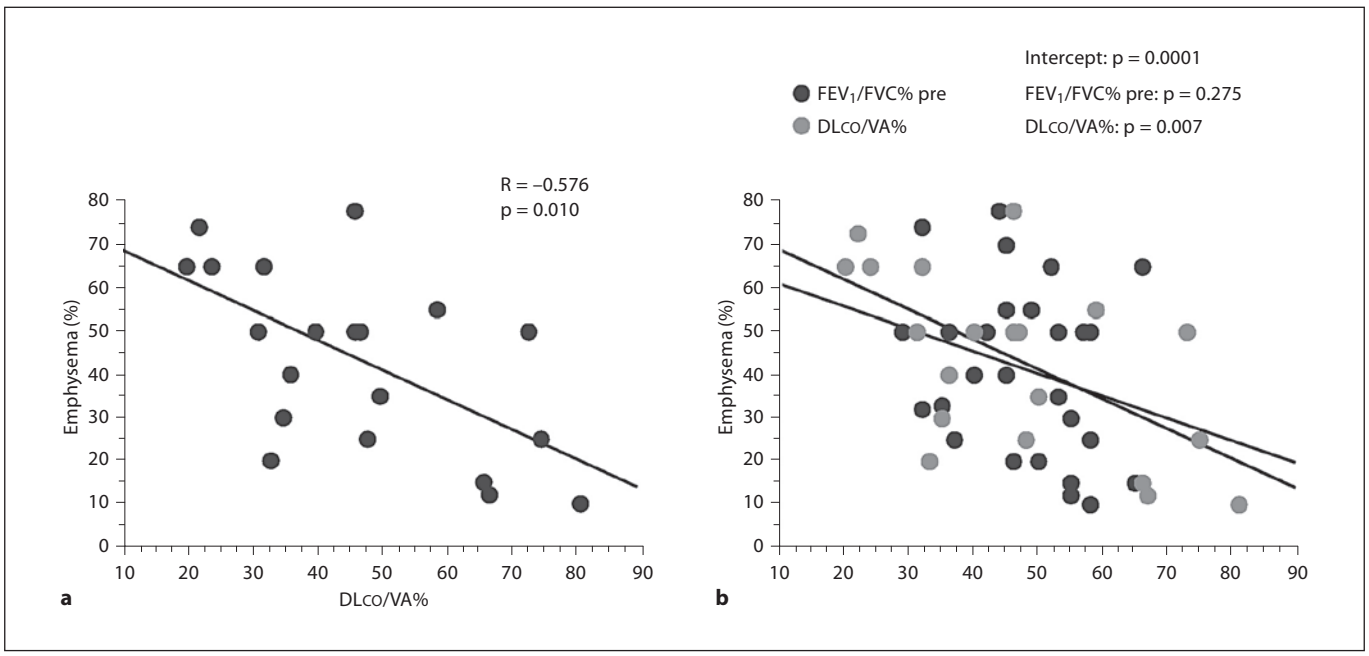

Fig. 3. Simple (**a**) and multiple regression (**b**) analysis in selected COPD patients with >10% HRCT scan score. **a** Simple regression analysis, including the percentage of emphysema and the DLCO/VA%, shows a significant inverse association between the percentage of emphysema and DLCO/VA% values. **b** Multiple regression analysis, including the percentage of emphysema as dependent variable and pre-bronchodilator (pre) FEV_1/FVC% as well as DLCO/VA% values as independent variables, shows a significant association between DLCO/VA% values and the degree of emphysema, as measured by HRCT scan score.

addition, as an original contribution, in a subgroup of patients with predominant emphysema (>10% HRCT scan score), the multivariate analysis showed the best correlation between HRCT scan-scored emphysema and DLCO/VA. This study helps to clarify which measures of pulmonary function can assess the extent of emphysema and which ones correlate best with HRCT scan results.

In agreement with previous studies [16, 17], we found that the extent of emphysema correlated inversely with pre- and post-bronchodilator FEV_1/FVC and directly with TLC. Furthermore, correlation between CT-evaluated emphysema and DLCO or DLCO/VA has also been documented by other authors [25–27].

We here observed a statistically significant correlation between HRCT-scored emphysema and number of pack/years smoked. These findings are in agreement with a larger study by Silverman and colleagues [28] that found a significant relationship between pack/years smoked and emphysema in a large group of COPD patients and siblings recruited, suggesting the presence of similar selection criteria adopted in our and Silverman's study.

In our study, multivariate analysis of pre-bronchodilator FEV_1/FVC and DLCO/VA correlated significantly with the percentage of emphysema. When our sample was split and patients with >10% of emphysema as estimated by the HRCT score were analyzed, DLCO/VA was more predictive of emphysema. A weaker association, albeit significant, was observed between DLCO% and the percentage of emphysema at both univariate and multivariate analysis. In fact, in emphysema, for a unitary VA, the alveolar-capillary surface area results showed a reduction proportionally to the extent of the emphysematous lesions. This can explain why DLCO/VA better reflects structural abnormalities at the alveolar level in patients with various degrees of emphysema [24, 26, 27]. These data suggest that, when monitoring COPD patients with emphysema, it is essential to include measurements of DLCO/VA% in the follow-up evaluation of this subgroup of COPD patients.

The HRCT evaluation of emphysema is at this moment the noninvasive method that best assesses the severity, extent and progression of emphysema in clinical practice. However, the technique is limited by several factors, and above all, is not suitable for monitoring the disease progression in patients with emphysema on account of the risk of radiation exposure, particularly in patients with a life expectancy >10 years [13]. Moreover, conflicting findings have been reported in the literature when different methods of evaluation of emphysema are compared [29–31]. We used a subjective method for the estimation of emphysema, i.e. visual score [22]. It has been reported that the analysis of visual scoring may lead to a systematic overestimation of emphysema [32, 33]. 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 [17]. Using 5- and 7-mm collimation with a pitch of 1.5, Park et al. [17] found good correlation between 3D assessment of both mean lung attenuation values and frequency distribution histograms of the whole lung compared with routine 2D analysis (r = 0.98–0.99) and visual scoring (r = 0.74–0.82). Visual and automated approaches to CT quantification of emphysema are imperfect. The absence of a readily available gold standard (i.e. morphometric estimation of emphysema extent) against which to compare CT quantification is a limitation in this field. Desai et al. [34] showed a better correlation between a composite physiologic index of two physiologic variables [FEV_1 and percent predicted VA (carbon monoxide transfer coefficient)] and the extent of visually estimated emphysema than with the automated scoring. Moreover, the authors found a strong correlation between the emphysema estimated visually and that quantified by automated scoring. They claimed that the discrepancy between the two methods, visual and automated, in estimating the extent of emphysema, is due to an underscoring by automated techniques rather than to overscoring on the part of visual estimation [34]. On this basis, we are confident that our visual score technique, performed by a well-trained operator, well represents the degree of emphysema in our sample of patients with COPD.

The correlation reported in the literature between the CT emphysema score and the pathological grade of emphysema is very high (r = 0.91) [32, 33, 35]. This correlation in in vivo measurements is reduced, ranging from 0.7 to 0.9. Some authors have observed that very mild emphysema could be missed in in vivo measurements. This may explain why a substantial number of patients in our present study with considerable smoking history, probably suffering from very mild emphysema, did not show detectable emphysema on HRCT [32–38].

In conclusion, 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 pulmo-

nary emphysema. The development, as we here propose, of a multiple regression model or 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.

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