Editorial

Pulmonary function tests and computed tomography lung attenuation in chronic obstructive pulmonary disease

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In the August 2015 issue of Radiology, Paoletti *et al*. reported the results of a study showing lack of linear correlation between pulmonary function tests (PFT) and lung attenuation on computed tomography (CT) in 132 patients with chronic obstructive pulmonary disease (COPD) (1). PFT were assessed according to the recommended and standardized procedures and measurements (2-4). Lung attenuation was measured with CT densitometry which unfortunately is not a standardized procedure both on the side of acquisition technique and on the side of image processing and measurements (5). In particular CT densitometry implies scanning the patient lying supine while she/he maintains breath-hold at end inspiration or expiration. Variables on the acquisition side include the inspiratory or expiratory lung volumes reached by the patient, number and collimation of sections, radiation dose and scanner calibration. Variables on the image processing and measurements side include application of reconstruction filters, automatic or semiautomatic segmentation of the lungs, correction for lung volume, automatic creation of histograms of density distribution and choice of measurement parameters to describe lung structural or functional status. Currently the main indications of lung CT densitometry in COPD include differentiation of emphysema and chronic bronchitis components in the single patient (alone or in combination with airways measurements) (6), monitoring progression of smoke-related pulmonary emphysema (7) and to be used as surrogate marker in trials assessing replacement therapy in alfa1-deficiency emphysema (8).

An additional field of application of lung densitometry in COPD has been evaluation of the correlation of the lung attenuation measurements with PFT and diffusing capacity of lung for carbon monoxide (D_{LCO}) (9-12). The percentage of lung area with CT attenuation values compatible with emphysema has been shown to be related to functional measurements of air flow obstruction (9-12), air trapping (11) and D_{LCO} (10,12). However CT lung attenuation in COPD results from intravoxel summation of reduced X-rays attenuation caused by overinflation and/or parenchymal destruction and from increased X-rays attenuation secondary to inflammatory changes (13). Accordingly, Paoletti *et al*. assumed that it is unlikely that the above pathophysiologic processes will sum to an output well described with a single linear function. Hence they assessed whether the relationship between pulmonary function and CT lung attenuation in COPD, which is traditionally described with single univariate and multivariate statistical models, could be more accurately described with a multiple model estimation approach. At univariate analysis, Paoletti *et al*. (1) found that the percent relative area at –950 Hounsfield Unit (HU) at inspiration ($\%LAA_{950insp}$) and the percent relative area at –910 HU at expiration ($\%LAA_{910exp}$) values higher than the mean value of their cohort of patients (19.1% and 22.0%) showed better correlation with percentage of predicted D_{LCO}% than with airflow obstruction [forced expiratory volume in 1 second (FEV_1)/vital capacity (VC)]. Conversely, $\%LAA_{950insp}$ and $\%LAA_{910exp}$ values lower than the mean value were correlated with FEV_1/VC but not with D_{LCO}%. Multiple model estimation performed with two multivariate regressions, each selecting the most appropriate functional variables (FEV_1/VC for mild parenchymal destruction, D_{LCO}% and functional

residual capacity for severe parenchymal destruction), predicted better than single multivariate regression both $\%LAA_{950insp}$ (R2=0.75 *vs.* 0.46) and $\%LAA_{910exp}$ (R2 =0.83 *vs.* 0.63).

Based on these results the authors drew three major conclusions.

First, COPD pulmonary function measurements are not linearly related to CT lung attenuation. In particular they outlined a twofold profile in which the relationships between some functional predictors and %LAA are not linear but varied depending on the degree of the CT densitometric alteration. In fact, for %LAA values compatible with greater parenchymal destruction a very weak association with FEV_1/VC was evidenced, whereas for %LAA values compatible with lower or absent parenchymal destruction, namely RA values lower than the mean, no significant association with D_{LCO}% was demonstrated. These data are in line both with failure of spirometric indexes of obstruction (e.g., FEV_1 and FEV_1/FVC) to correlate with presence and the severity of emphysema as reflected by quantitative CT evaluation (11) and with the great accuracy of D_{LCO}% in the identification of CT-detected emphysema (14).

Second, since the twofold profile heavily affects the performances of traditional (single) multivariate regression models, a multiple model approach that combines measurements of airflow obstruction (FEV_1/VC), overinflation (FRC%), and parenchymal destruction (D_{LCO}%) can more accurately predict the inspiratory and expiratory %LAA over a wide range of values.

Third, the complexity of COPD cannot be expressed with a simple measurement of expiratory airflow obstruction (15,16).

The paper of Paoletti *et al.* (1) contributes to the existing literature for two reasons. First it adds to data exploring use of PFT in predicting the CT attenuation variables (12). This is useful in clinical practice and in clinical or pharmacological studies in which CT is not feasible or cost-effective. Second, it provides potentially valuable information to be incorporated in modeling the complex pathophysiology of COPD as apparent based on clinical, functional, laboratory and CT features (16).

The study has some limitations concerning data analysis, CT acquisition technique and lung densitometry.

The study patients were divided according to the distribution of densitometric measurements, namely $\%LAA_{950insp}$ and $\%LAA_{910exp}$, in a population of COPD patients whose clinical-functional severity according to GOLD classification was not provided. Since densitometry distribution is conceivably influenced by the severity of COPD as reflected in GOLD classification this omission is remarkable. Moreover one might argue that demonstration of a non-linearity of the relationship between PFT and lung attenuation values would have required application of a non-linear model rather than two linear models after arbitrary dichotomization of the population based on densitometry results.

Paoletti *et al.* (1) did not control for volume at acquisition and did not perform volume normalization of the lung attenuation data (17). Moreover they adopted "old" densitometric measurements, namely RA-950 HU for inspiratory scans and RA-910 HU for expiratory scans. In particular the former showed a weaker correlation with macroscopic and microscopic morphometry evidence of emphysema as compared to RA-960 HU and RA-970 HU (18) in inspiratory scans. As well Schroeder *et al.* (11) proposed another threshold for air trapping in expiratory scans, namely -856 HU. This choice may have affected the capability of PFT to predict attenuation values they observed in the correlation and single multivariate regression analyses.

However my main remark is that, due the uncertain clinical-functional profile of the COPD patients and the non-standardization of the CT acquisition and densitometry, the results of this study cannot be generalized, especially if, as in the purpose of the Authors, PFT and D_{LCO}% are used to predict lung attenuation values in cases in which CT is not feasible or cost-effective. In fact the predictive values of PFT and D_{LCO}% they reported using machine learning approach strictly pertain to the patients characteristics, CT acquisition technique and lung densitometry procedure considered.

Notwithstanding the above limitations, Paoletti *et al.* (1) have to be commended for their study. Further investigations, hopefully incorporating airway evaluation beside lung attenuation, are worthy to disentangle the relationship among PFT, D_{LCO}% and CT findings in COPD.

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Footnote

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