Arch Bronconeumol. 2010;**46(2)**:56-63

ARCHIVOS DE BRONCONEUMOLOGIA

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Original Article

Severity Related Differences in Lung Attenuation in Men With COPD

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ARTICLE INFO

Article history:
Received May 16, 2009
Accepted September 14, 2009
Available online 5 November 2009

Keywords:
COPD
Computed tomography
Pulmonary function test

ABSTRACT

Background and objectives: We compare the inspiratory and expiratory regional lung densities between different levels of COPD severity (as assessed by the GOLD scale and by the BODE index), and to assess the relationship between regional lung densities and functional lung parameters.
Patients and methods: Fifty-five stable moderate-severe COPD men were selected. Functional evaluation included dyspnoea scale, blood gases, spirometry, plethysmography, diffusing capacity and six-minute walk test. Severity was classified according the GOLD scale and the BODE index. High resolution computed tomography (HRCT) scans of the entire lung at full inspiration and two sections at full expiration were obtained. Densitometry software was used to calculate the densities of the lung areas.
Results: Inspiratory and expiratory mean lung densities (MLD) of the lower lobes were significantly lower in very severe and severe COPD patients than in moderate patients. In contrast, we only found differences between the upper lobe MLD values of moderate and severe COPD patients. Inspiratory and expiratory HRCT densities were similar among all BODE quartiles, for both the upper and lower lobes. In a multiple regression analysis, airway obstruction parameters were mainly related to the expiratory MLD of the lower lobes, whereas lung hyperinflation parameters were predicted by the inspiratory MLD of the lower lobes. Lastly, diffusion capacity was independently related to the expiratory/inspiratory MLD of the lower lobes and to the inspiratory MLD of the upper lobes.
Conclusions: There are differences in lung attenuation measurements by HRCT between the varying levels of COPD severity as assessed by the GOLD scale.

Diferencias en función de la gravedad de la atenuación pulmonar en varones con EPOC

Palabras clave:
EPOC
Lactatodeshidrogenasa
Isoenzimas
Músculo esquelético

RESUMEN

Introducción: El objetivo del estudio ha sido comparar la atenuación pulmonar inspiratoria y espiratoria en varones con enfermedad pulmonar obstructiva crónica (EPOC), según la gravedad, así como valorar la relación entre la atenuación del parénquima y la función pulmonar.
Pacientes y métodos: Se seleccionó a 55 varones con EPOC moderada-muy grave y clínicamente estables. Se les realizaron gasometría arterial, espirometría, pletismografía, difusión de monóxido de carbono y prueba de la marcha. La gravedad de la EPOC se clasificó en función de la escala GOLD y del índice BODE. Se realizó una tomografía computarizada de tórax de alta resolución en inspiración y espiración, utilizando un programa informático específico para medir la atenuación de las diferentes áreas pulmonares.
Resultados: La atenuación de los lóbulos inferiores fue menor en pacientes con EPOC grave y muy grave que en casos con enfermedad moderada, tanto en inspiración como en espiración. En los varones con EPOC moderada y grave se detectaron diferencias en la atenuación media de los lóbulos superiores. No se hallaron diferencias en función de los cuartiles del índice BODE. Los parámetros de obstrucción de la vía aérea se relacionaron principalmente con la atenuación de los lóbulos inferiores en espiración, mientras que los parámetros de hiperinsuflación se correlacionaron con la atenuación en inspiración. Por último, la capacidad de difusión se relacionó de forma independiente con el valor de atenuación espiratoria/inspiratoria de los lóbulos inferiores y la atenuación de los lóbulos inferiores en inspiración.
Conclusiones: Se observan diferencias en la atenuación pulmonar entre los diferentes grados de gravedad de la EPOC establecidos según la clasificación GOLD.

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0300-2896/$ - see front matter

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a lung function deficit with airway obstruction,[1-4] although clinically there is a significant phenotype heterogeneity.[5,6] Additional to conventional assessment of the disease,[7] it has recently been proposed that the BODE index be used (based on the degree of limitation of airway flow, dyspnoea, exercise tolerance and body mass index) to predict mortality.[8]

High resolution computed tomography (HRCT) is a very useful non-invasive tool to assess emphysema. It has been shown that there is correlation between lung parenchyma density determined by means of HRCT and pathological changes in tissue samples[9,10] and pulmonary function deficits (obstruction of airflow and diffusion capacity).[11,12] Furthermore, although HRCT measurements during inspiration show the degree of destruction due to emphysema, the densitometry analysis on expiration and the expiratory/inspiratory ratio of lung density seem to reflect peripheral airway obstruction and air entrapment.[11-13]

Although it is possible to determine, using HRCT, objective indicators of lung density, few studies have assessed their relationship with the severity of the disease. In patients with asthma, lung density seen on HRCT is related to the severity of the disease and decreases during exacerbations.[14,15] A previous study did not find any differences in lung density during inspiration or expiration in 10 patients with slight COPD and a heterogenous group of patients with moderate or severe COPD – stages II-IV of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[16] Moreover, the differences in lung density between men with moderate and severe COPD have not been investigated. The aim of this study was to compare lung density of patients with different degrees of COPD, assessed by means of airflow obstruction or a multidimensional classification system (BODE Index). We have also assessed the relationship between lung density and lung function parameters in cases of moderate-very severe COPD.

Patients and Methods

Patients

We carried out consecutive clinical exams on 55 men with moderate-very severe COPD – forced expiratory volume in the first second (FEV_1) after administration of a bronchodilator < 80% of the predicted value and FEV_1/forced vital capacity (FVC) < 70% -in stable conditions.[7] Exclusion criteria were: history of asthma, other active pulmonary disease, mental or physical disability or other significant diseases that could contribute to dyspnoea or exercise limitation, such as congestive heart failure, ischaemic or valve cardiopathy or neuromuscular disease. None of the patients had suffered a COPD exacerbation or infection of upper airways during the 4 previous weeks, and none had showed significant reversibility after bronchodilator administration (> 12% basal FEV_1 or > 200ml). Nor had they received treatment with oral corticosteroids during the last 3 months as a minimum. They all gave their informed consent in writing and the Ethics Committee approved the study.

Procedures

All the patients abstained from using short or prolonged action bronchodilators for 6 and 12 hours, respectively, and discontinued their Tiotropium 24 hours before. None of the patients consumed caffeine or smoked during the 2 hours prior to the lung function tests. The patients were weighed barefoot and in their underclothes, and their body mass index was calculated.

Functional dyspnoea was assessed by means of the Medical Research Council (MRC)[17] modified dyspnoea scale, which includes 5 degrees of physical activity that cause dyspnoea.

All lung function measurements were carried out as described in a previous paper,[18] with the patients sitting down and always in the same order, allowing sufficient rest between one manoeuvre and the next one. All the procedures were performed by the same technician, who was unaware of the results. Measurements of arterial blood gasses and pH at rest were taken using a blood gas analyser (ABL330, Radiometer, Copenhagen, Denmark) while the patient breathed room air. Slow forced spirometry studies were performed using a pneumotachograph, and static air volumes were measured with a constant volume whole-body plethysmograph (MasterLab Body, Jaeger, Würzburg, Germany), according to the directives of the European Respiratory Society.[19] Inspiratory capacity (IC) was measured according to the O'Donnell and Web protocol,[20] and IC/TLC (inspiratory capacity/total lung capacity) was used as a measurement of hyperinsufflation at rest. The diffusing capacity for carbon monoxide (DLCO) was measured by means of a single respiration (MasterLab)[21] and was corrected for haemoglobin values (DLCOc).[22] Predictive values for lung function parameters were determined based on those published by the European Coal and Steel Community (ECSC).[19, 23]

The 6 min walk test was carried out in a 50m corridor, according to the guidelines of the American Thoracic Society.[24] The best result of 2 tests was taken, separated by a minimum 30 min interval.

The patients were classified in 3 groups based on the severity of their COPD according to the GOLD classification.[7] Stage II COPD with moderate airway limitation (FEV_1 50–80% of predicted value), stage III (FEV_1 30–50% of predicted value) and stage IV (FEV1 < 30% of predicted value). Furthermore, the predicted percentage of FEV_1 (FEV_1%), the body mass index, the 6 min walk test, and the result of the MRC scale are all included in the BODE index and the quartiles of these calculated.[8]

Computed tomography was performed in a supine position using a single-slice spiral scanner (Somaton Plus 4A, Siemens, Erlangen, Germany) with a scan time of 0.75s. First an HRCT was done of the whole lung during a complete inspiration, with 1mm slices and table movements of 10mm. Subsequently, 2 lung slices during complete expiration were studied: at the level of the aortic arc, and below, at the level of the confluence of the inferior pulmonary veins.

Voltage and electric current were adjusted to the weight of each patient, with variations between 120-140kW and 200-300mA. All the images were obtained with an appropriate window to see the mediastinum and lung parenchyma (this last with a window of 1,500 and a window centre of 500HU). The field of vision was adjusted to the external cortex of the ribs to optimize the matrix. The Siemens Somaton Plus 4 computer program for lung densitometry was used with these limits (−800/−1,024HU) to calculate densities, after validating densitometry values with phantoms. We established the area with a freehand drawing of the region of interest, then we established limits (in HU) and the computer program calculated the attenuation as mean lung density (MLD) of the lower and upper lobes. The middle lobe and the lingula were not included because the CT scans were taken lying down and, therefore, there would have been greater air entrapment in these areas. The time between lung function tests and CT scans was never longer than 3 days.

Statistical Analysis

Data are expressed as mean ± standard deviation. The χ^2 was used to assess frequencies. Comparisons between groups were performed by variance analysis with multiple post hoc comparisons made using the Bonferroni test. Relations between variables were determined using Pearson's correlation analysis and multiple linear regression

analysis.[25] Said analyses were carried out using a Windows SPSS version 11.0 statistical analysis program (SPSS Inc., Chicago, IL, USA). In all cases values of $p < .05$ were considered significant.

Results

The characteristics of the patients and the results of the lung function tests can be seen in Table 1. In Table 2 it is possible to see the results of HRCT density-mask analysis according to the GOLD classification. Lower lobe MLD on inspiration and expiration were lower in patients with very severe or severe COPD than in those with moderate disease. On the other hand the only differences in upper lobe MLD were seen between patients with moderate and severe COPD. MLD on inspiration and expiration and the upper/lower ratios were similar in the 3 groups classified according to degree of EPOC severity.

Determination of the BODE index made it possible to classify 17 patients in quartile 1, 19 in quartile 2, 13 in quartile 3 and 6 in quartile 4 (Table 3). Attenuation during inspiration and expiration was similar in the 4 quartiles, both for upper and lower lobes. No differences were found in expiratory/inspiratory or upper/lower ratios for the 4 degrees of severity according to the BODE index.

The results of the correlation analysis between lung density and HRCT and functional parameters can be seen in Table 4. The parameters related to airflow limitation, air entrapment and lung hyperinsufflation are mainly related to lung density both of the upper and lower lobes (Figs. 1 and 2). On the other hand, the DLCOc related to alveolar volume (Fig. 3) was mainly related to upper lobe density, and lower lobe expiratory/inspiratory ratio ($r = -0.557$; $p < .001$) and with upper/lower inspiratory and expiratory ratios ($r = -0.496$; $p < .01$, and $r = -0.336$; $p < .05$, respectively).

Table 1
Clinical and Functional Characteristics of Men with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Classification

	Stage II, moderate (n = 16)	Stage III, severe (n = 20)	Stage IV, very severe (n = 19)
Age (years)	66 ± 7	64 ± 8	62 ± 7
Height (cm)	166 ± 6	165 ± 6	167 ± 8
Weight (kg)	77 ± 12	77 ± 14	74 ± 12
Body mass index (kg/m^2)	28.0 ± 3.2	27.9 ± 4.1	26.2 ± 2.8
Former smokers and smokers	87	70	74
Pack-years	43 ± 12	47 ± 15	110 ± 104[a]
Years since diagnosis	9 ± 6	11 ± 11	7 ± 2
FVC (l)	2.76 ± 0.65	2.73 ± 0.54	2.56 ± 0.69
FVC (% of predicted value)	80 ± 16	75 ± 10	67 ± 15
FEV_1 (l)	1.72 ± 0.40	1.11 ± 0.19[c]	1.13 ± 0.67[c]
FEV_1(% of predicted value)	62 ± 7	39 ± 5[c]	35 ± 9[c]
FEV_1/FVC (%)	62 ± 6	44 ± 7[c]	42 ± 15[c]
TLC (% of predicted value)	93 ± 15	114 ± 9[c]	111 ± 18[b]
FRC (% of predicted value)	103 ± 23	129 ± 29[a]	143 ± 34[b]
RV(% of predicted value)	115 ± 33	182 ± 29[c]	181 ± 45[c]
RV/TLC (%)	49.2 ± 8.0	60.2 ± 6.8[c]	59.1 ± 7.5[b]
IC/TLC (%)	37.8 ± 8.9	29.9 ± 8.2[a]	30.1 ± 7.6[a]
DLCOc (% of predicted value)	101 ± 20	90 ± 37	52 ± 13[b]
DLCOc/VA (% of predicted value)	105 ± 29	96 ± 41	66 ± 19[b]
pH	7.41 ± 0.02	7.40 ± 0.02	7.41 ± 0.02
PaO_2 (mmHg)	67.8 ± 11.3	61.8 ± 8.3	59.7 ± 8.5
$PaCO_2$ (mmHg)	41.0 ± 6.9	43.2 ± 4.5	39.8 ± 5.7
Distance walked in 6 min (m)	475 ± 83	425 ± 77	359 ± 97[b,d]
MRC	2 ± 1	2 ± 1	3 ± 1[a]

Data are expressed as mean ± standard deviation. IC: inspiratory capacity; DLCOc: diffusing capacity for carbon monoxide corrected for haemoglobin; E/I: Forced expiratory volume in the first second; FRC: functional residual capacity; FVC: forced vital capacity; MRC: Medical Research Council dyspnoea scale; $PaCO_2$: Arterial pressure *of* carbon dioxide; PaO_2: Arterial pressure of oxygen; TLC: Total lung capacity; AV: Alveolar volume; RV: Residual volume.

[a] $p < .05$ for stage II.
[b] $p < .01$ for stage II.
[c] $p < .001$ for stage II.
[d] $p < .05$ for stage III.

Table 2
High Resolution Computed Tomography Measurements in Men with COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification

	Stage II (n = 16)	Stage III (n = 20)	Stage IV (n = 19)
Upper lobe MLD on inspiration (HU)	−922 ± 24	−942 ± 15[a]	−936 ± 22
Lower lobe MLD on inspiration (HU)	−912 ± 26	−930 ± 11[a]	−932 ± 23[b]
Upper lobe MLD on expiration (HU)	−903 ± 27	−926 ± 22[a]	−920 ± 27
Lower lobe MLD on expiration (HU)	−893 ± 25	−912 ± 15[a]	−918 ± 24[b]
Upper lobe MLD E/I ratio	0.979 ± 0.011	0.983 ± 0.011	0.983 ± 0.014
Lower lobe MLD E/I ratio	0.980 ± 0.022	0.981 ± 0.011	0.985 ± 0.013
Upper/lower lobe MLD ratio in inspiration	1.012 ± 0.022	1.013 ± 0.018	1.005 ± 0.022
Upper/lower lobe MLD ratio in expiration	1.012 ± 0.016	1.016 ± 0.022	1.003 ± 0.021

Data are expressed as mean ± standard deviation. E/I: expiratory/inspiratory; HU: Hounsfield units; MLD: mean lung density:

[a] $p < .05$ for stage II.
[b] $p < .01$ for stage II.

Table 3
Measurements Taken using High Resolution Computed Tomography, during Inspiration and Expiration, according to the BODE Index

	Quartile 1 (n = 17)	Quartile 2 (n = 19)	Quartile 3 (n = 13)	Quartile 4 (n = 6)
Age (years)	66 ± 7	63 ± 9	63 ± 6	64 ± 7
Body mass index (kg/m^2)	27.5 ± 2.9	27.4 ± 4.1	26.7 ± 4.1	27.6 ± 1.3
FVC (% of predicted value)	81 ± 15	71 ± 12	74 ± 11	64 ± 21
FEV_1(% of predicted value)	59 ± 10	41 ± 9[c]	36 ± 7[c]	30 ± 3[c]
FEV_1/FVC (%)	58 ± 11	48 ± 11	39 ± 10[c]	41 ± 19[a]
TLC (% of predicted value)	99 ± 16	110 ± 18	116 ± 18	112 ± 20
FRC (% of predicted value)	115 ± 27	122 ± 29	132 ± 34	174 ± 26[b,d]
VR (% of predicted value)	129 ± 42	167 ± 42	184 ± 48[a]	188 ± 43
VR/TLC (%)	50.8 ± 8.8	57.8 ± 7.1	60.3 ± 7.3[a]	61.9 ± 9.0
CI/TLC (%)	37.5 ± 8.3	29.9 ± 9.0	30.0 ± 7.8	29.5 ± 6.5
DLCOc (% of predicted value)	89 ± 19	76 ± 26	65 ± 29	40 ± 10[b]
DLCOc (% of predicted value)	103 ± 29	88 ± 30	66 ± 22[a]	40 ± 14[b]
pH	7.42 ± 0.02	7.40 ± 0.01	7.42 ± 0.02	7.41 ± 0.01
PaO_2 (mmHg)	71.7 ± 8.1	61.5 ± 8.5	56.6 ± 7.0	53.4 ± 6.1
$PaCO_2$ (mmHg)	38.2 ± 3.6	43.8 ± 7.0	39.4 ± 1.9	40.2 ± 3.1
Upper lobe MLD on inspiration (HU)	–927 ± 24	–937 ± 16	–938 ± 22	–939 ± 28
Lower lobe MLD on inspiration (HU)	–915 ± 26	–930 ± 12	–924 ± 26	–941 ± 12
Upper lobe MLD on expiration (HU)	–909 ± 27	–922 ± 22	–918 ± 31	–927 ± 29
Lower lobe MLD on expiration (HU)	–897 ± 25	–915 ± 18	–909 ± 29	–923 ± 9
Upper lobe MLD E/I ratio	0.981 ± 0.011	0.983 ± 0.010	0.979 ± 0.017	0.988 ± 0.007
Lower lobe MLD E/I ratio	0.981 ± 0.021	0.983 ± 0.012	0.983 ± 0.010	0.981 ± 0.018
Upper/lower lobe MLD ratio in inspiration	1.013 ± 0.021	1.008 ± 0.017	1.015 ± 0.023	0.998 ± 0.024
Upper/lower lobe MLD ratio in expiration	1.013 ± 0.017	1.008 ± 0.022	1.010 ± 0.018	1.005 ± 0.031

Data are expressed as mean ± standard deviation. IC: inspiratory capacity; DLCOc: diffusing capacity for carbon monoxide corrected for haemoglobin; E/I: expiratory/inspiratory; FEV_1: forced expiratory volume in the first second; FRC: functional residual capacity; FVC: forced vital capacity; HU: Hounsfield units; MLD: mean lung density; $PaCO_2$: arterial pressure of carbon dioxide; PaO_2: arterial pressure of oxygen; TLC: total lung capacity; AV: alveolar volume; RV: residual volume.

[a] $p < .05$ for quartile 1.

[b] $p < .01$ for quartile 1.

[c] $p < .001$ for quartile 1.

[d] $p < .05$ for quartile 2.

Table 4
Correlation Coefficients between Lung Density seen on High Resolution Computed Tomography and Clinical Characteristics of Patients with COPD

	Upper lobes			Lower lobes		
	Inspiratory MLD	Expiratory MLD	MLD E/I ratio	Inspiratory MLD	Expiratory MLD	MLD E/I ratio
Age (years)	0.385[b]	0.403[b]	–	–	0.272[a]	–0.375[b]
FEV_1 (% of predicted value)	0.345[a]	0.333[a]	–	0.473[c]	0.492[c]	–
FEV_1/FVC (%)	0.529[c]	0.474[b]	–	0.439[b]	0.556[c]	–
TLC (% of predicted value)	–0.629[c]	–0.562[c]	–	–0.497[c]	–0.527[c]	–
FRC (% of predicted value)	–0.568[c]	–0.539[c]	–	–0.489[b]	–0.541[c]	–
RV (% of predicted value)	–0.624[c]	–0.623[c]	0.309[a]	–0.613[c]	–0.604[c]	–
RV/TLC (%)	–0.365[a]	–0.303[a]	–	–0.537[c]	–0.396[b]	–
IC/TLC (%)	–	–	–	0.315[a]	–	–
DLCOc (% of predicted value)	0.469[b]	0.501[b]	–	–	0.365[a]	–0.557[c]

IC: inspiratory capacity; DLCOc: diffusing capacity for carbon monoxide corrected for haemoglobin; FEV_1: forced expiratory volume in the first second; FRC: functional residual capacity; FVC: forced vital capacity; MLD: mean lung density; TLC: total lung capacity; VA: alveolar volume; VR: residual volume.

[a] Significant correlation with $p < .05$.

[b] Significant correlation with $p < .01$.

[c] Significant correlation with $p < .001$.

In the multiple regression analysis FEV_1% and the FEV_1/FVC ratio were related to MLD of the lower lobes on expiration ($r^2 = 0.242$; $p < .001$, and $r^2 = 0.306$; $p = .001$, respectively). On the other hand lower lobe MLD on inspiration was the only independent variable related to the residual volume/TLC ratio ($r^2 = 0.288$; $p < .001$) and IC/TLC ($r^2 = 0.099$; $p < .05$). Last, DLCOc related to alveolar volume (in percentages of predicted value) was independently related to lower lobe expiratory/inspiratory MLD ratio and upper lobe inspiration MLD ($r^2 = 0.415$; $p < .001$).

Discussion

The main result of this study is the observation that attenuation of lung parenchyma assessed by HRCT is different according to the severity of COPD, established according to the GOLD classification. On the other hand, the BODE index does not distinguish between patients with different degrees of lung parenchyma attenuation. In spite of the fact that many studies have addressed the capability of CT to quantify lung damage with any degree of exactitude by correlating lung density with lung function,[26,27] the differences in lung density of patients with moderate and severe COPD had not been investigated.

Several methods have been developed to objectively quantify lung emphysema: The measurement of mean lung density, the areas of the lung with lower values of density to predetermined thresholds, and a predetermined percentile of the distribution curve of lung density.

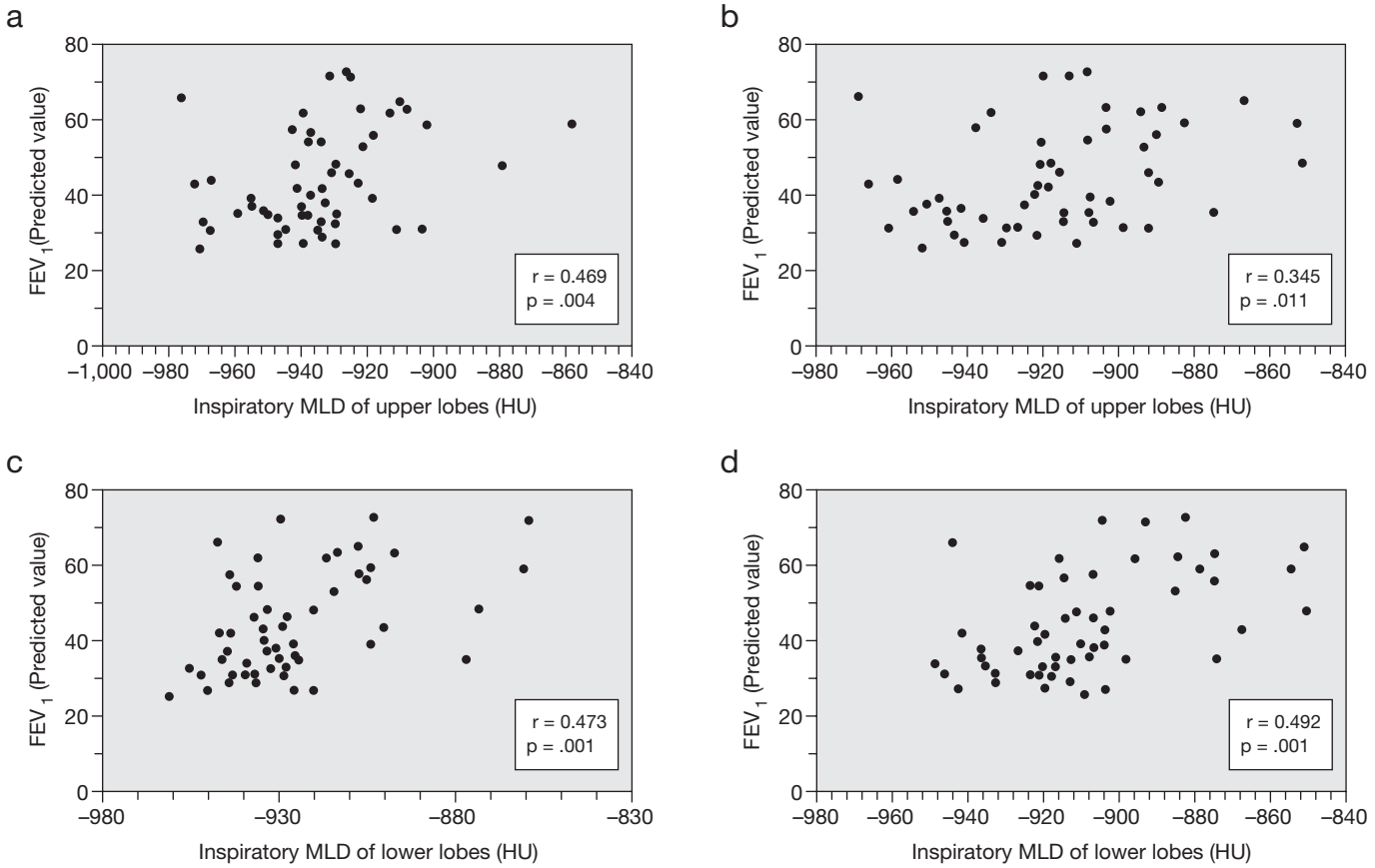

Figure 1. Relation between forced expiratory volume in the first second, as a percentage of predicted value (FEV_1%), and lung density. MLD: mean lung density.

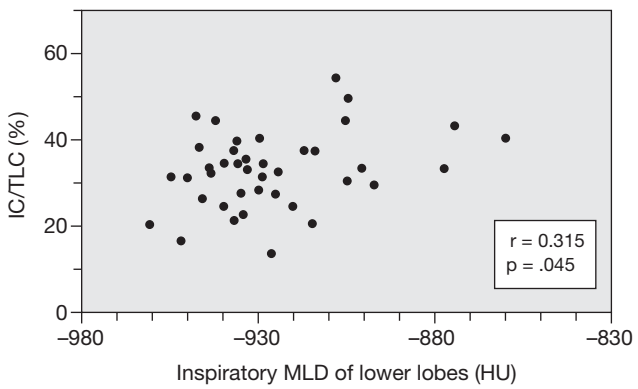

Figure 2. Relation between inspiratory capacity and total lung capacity ratio (IC/TC) and densities of lung density. MLD: mean lung density.

In this study, a lung densitometry computer program was used to calculate upper and lower lobe mean lung density during profound inspiration and total expiration.

MLD is a CT parameter frequently used to assess emphysema.[26] Several studies have shown advantages with reference to other CT parameters for emphysema prediction. For example, Moroni et al[28] compared lung density measurements obtained with and without control spirometry using HRCT. In said study, MLD measurements based on the scans performed with and without spirometry controls were similar, whereas other CT measurements did not coincide. Furthermore, MLD is a parameter that is still used repeatedly in recent studies, for example in 2009, Akira et al[29] published a study in the *American Journal of Roentgenology* that had the aim of determining if the measurements of lung density on inspiration and expiration, obtained from 3D lung reconstructions, reflect the severity of COPD, for this, a multislice CT was performed, subsequently processed in 3D, during complete inspiration and expiration, of 76 patients with COPD, and mean inspiratory and expiratory lung densities were measured, as also expiratory/inspiratory lung density ratio.

Therefore, we decided to use this parameter calculating upper and lower lobe mean density during profound inspiration and total expiration. We established a limit of −800/−1,024HU, assuming that this range would cover all degrees of lung emphysema. Although density values below -910HU have been considered adequate to objectively establish the presence of emphysema using HRCT, we chose lower valued to ensure the inclusion of hypothetical patients with subtle changes seen with HRCT but with clinical COPD. According to some studies, lung density determined by scans during complete inspiration is of about −800HU (−806HU) in people with no ventilation deficiency, so below this limit there should only be minimal emphysematous changes. Furthermore, we included 2 slices in complete expiration for each patient and since lung density values during expiration increased[26] (there is a relatively large amount of vessels and connective tissue), we needed a larger interval.

We used spiral CT with a high frequency reconstruction algorithm. We included 2 complete spiral slices because some authors had pointed out that the scans obtained during complete expiration provide more functional information than those obtained during complete inspiration.[11]

In our study, quantification by means of lung parenchyma HRCT allowed us to differentiate between moderate, severe and very severe

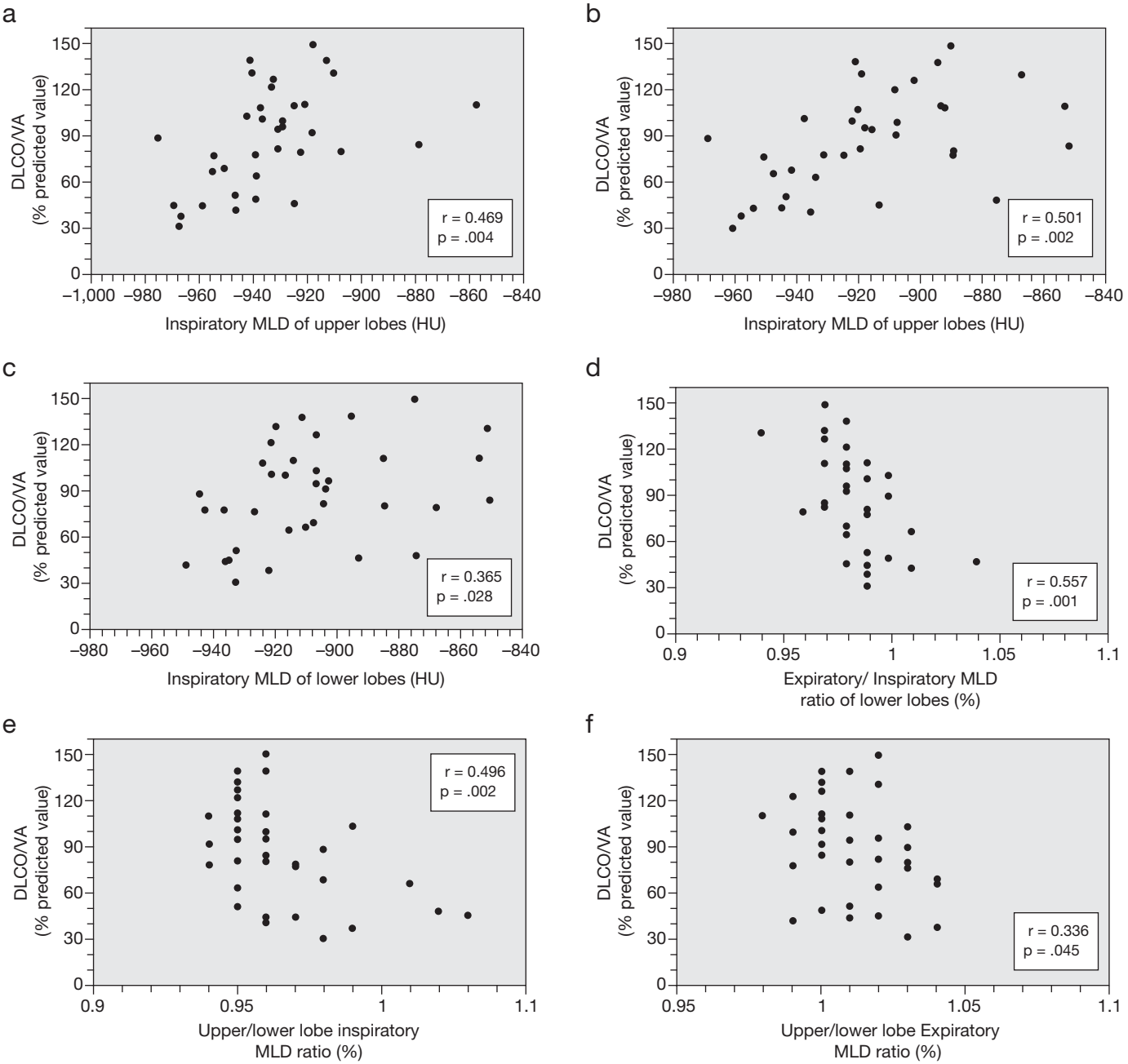

Figure 3. Relation between the diffusing capacity for carbon monoxide corrected for haemoglobin (DLCOc) and related to alveolar volume, as a percentage of predicted value (DLCOc/VA%), and densities of lung attenuation. MLD: mean lung density.

degrees of the GOLD classification. We did not include patients with slight COPD because their morphological and functional alterations are still very subtle. In our study, the impossibility of differentiating between some GOLD stages based on upper lobe density values could be attributed simply to the small size of the sample. However, and whenever the main difference between severe and very severe COPD is the presence of respiratory failure, our results could also indicate the very scarce contribution of the upper lobes to gas exchanges in patients with COPD.[30]

The relation between lung density and the main GOLD classification values (FEV_1 and FEV_1/FVC ratio) has been documented in other studies.[10,11,31,32] However, up to now it had not been documented if different FEV_1 thresholds would serve to differentiate between different degrees of lung density.

Furthermore, our study allowed us to assess the effect of regional lung differences and the influence of image acquisition during inspiration-expiration on the relation between density and lung function. Nakano et al[31] have already shown that airflow limitation was related to the percentage of low density of the internal segment of the lower lobe, whereas gas transfer was related to the internal segment of the upper lobes. Other authors have observed that HRCT measurements during expiration, in comparison with HRCT during inspiration, are more closely related to lung function in smokers with and without airway obstruction.[16]

In our patients, multiple regression analysis revealed that lung measurements that reflect airway obstruction (FEV_1 and FEV_1/FVC) are correlated with lower lobe expiratory MLD, whereas air entrapment and lung insufflations indexes (residual

volume/TLC and IC/TLC) are correlated with lower lobe MLD during inspiration.

Airway obstruction in patients with COPD is due, in part, to an increase of the intrinsic resistance of the airways and a loss of lung elastic retraction. In these patients, the calibre of the intraparenchymal airways is expected to be much less during expiration than during inspiration, since the walls of the airways are less compressible, or the traction force of the pulmonary parenchyma is reduced.

On the other hand, the parameters observed with HRCT on inspiration could represent the relative extension of lung hyperinsufflation, which is the main consequence of expiratory airflow limitation and has important clinical implications. In patients with COPD, IC at rest, a reflection of lung volume at the end of expiration, is correlated with the exercise capacity measured by maximum oxygen take-up and retention of carbon dioxide during exercise.[33] We used the IC/TLC ratio because it reflects not only the degree of lung hyperinsufflation, but also the functional reserve in patients with COPD.[34] It is interesting to note that 2 recent prospective studies have shown that hyperinsufflation contributes to COPD mortality. Nishimura et al[35] found that lung hyperinsufflation, expressed as a residual volume/TLC ratio, is a strong mortality predictive variable. Following the same line of thought, Casanova et al[34] showed that the IC/TLC ratio predicted mortality in a cohort of 689 patients with COPD and a mean follow-up of 34 months. Furthermore, the IC/TLC ratio predicted mortality independent of the BODE index.

Contrary to what has been observed with the GOLD classification, no differences were found in lung density between different quartiles of the BODE index, probably due to the participation of extrapulmonary factors in this prognostic score. However, a recent study has determined that patients with emphysema determined by HRCT had a higher BODE score than patients without emphysema determined by HRCT and the controls.[36] Several factors explain these discrepancies. First, the method used to quantify emphysema was different to the one we used: They defined emphysema as more than 15% of the lung showing attenuation values below−950HU, which in our opinion could underestimate subtle emphysematous changes seen with HRCT. Therefore, some patients were not considered to have emphysema. Second, they used a volumetric reconstruction algorithm, whereas in this study we used a sequential one to study and quantify the attenuation of lung parenchyma, since we considered this more appropriate for a study of lung interstitium and, in consequence, lung emphysema. Furthermore, the number of patients with emphysema documented by HRCT in the study performed by these authors was not large (11 patients). Finally, the aim of this study was not to differentiate between the degrees of clinical COPD using HRCT, so their objective was different to ours. We believe that more studies must be performed to determine if there is correlation between BODE quartiles and HRCT findings.

Last, we hope these results are helpful for the radiological determination of the severity of COPD, which would help physicians to carry out a better classification of each patient in a group according to the severity of their COPD, and this would lead to more appropriate information and treatment.

Conflict of Interests

The authors state they have no conflict of interests.

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