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Pulmonary stereology in chronic obstructive pulmonary disease: pulmonary functional imaging examination

Estereología pulmonar en enfermedad pulmonar obstructiva crónica: exploración funcional pulmonar por imagen

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ABSTRACT. Computed tomography images are increasingly used in order to characterize lung diseases more accurately. A good correlation with lung function has been described, especially in chronic obstructive pulmonary disease. Spirometry is currently the gold standard for chronic obstructive pulmonary disease diagnosis, but computed tomography has been positioned to identify early disease and to identify progression in established disease. In the last decade, the functional evaluation of chronic obstructive pulmonary disease by computer tomography has improved diagnostic certainty, evaluation and prediction of progression. Moreover, it allows selecting patients for therapeutic interventions. Multiple metrics are used as prognostic-related imaging biomarkers in chronic obstructive pulmonary disease and have been correlated with respiratory function tests. This review aims to analyze the current and future role of CT in COPD.

Keywords: stereology, chronic obstructive pulmonary disease, spirometry, computed tomography.

RESUMEN. Las imágenes obtenidas por tomografía computarizada se utilizan cada vez más para caracterizar con mayor precisión las enfermedades pulmonares. Se ha descrito una buena correlación con la función pulmonar, especialmente en la enfermedad pulmonar obstructiva crónica. Actualmente, la espirometría es el estándar de referencia en el diagnóstico de la enfermedad pulmonar obstructiva crónica, pero la tomografía computarizada se ha posicionado como método de imagen para identificar enfermedad temprana y progresión en enfermedad establecida. En la última década la evaluación funcional de la enfermedad pulmonar obstructiva crónica por tomografía computarizada ha permitido incrementar la certeza diagnóstica, la evaluación y la predicción de la progresión de la enfermedad. Además, proporciona una mejor selección de pacientes para intervenciones terapéuticas. Múltiples métricas de tomografía computarizada se usan como biomarcadores de imagen en la enfermedad pulmonar obstructiva crónica relacionadas con el pronóstico y se han correlacionado con las pruebas de función respiratoria. La presente revisión pretende analizar el papel actual y futuro de la tomografía computarizada en la evaluación de la enfermedad pulmonar obstructiva crónica.

Palabras clave: estereología, enfermedad pulmonar obstructiva crónica, espirometría, tomografía computada.

Abbreviations:

CT = computed tomography.
COPD = chronic obstructive pulmonary disease.
PFT = pulmonary function test.
DLco = Diffusing capacity of the lungs for carbon monoxide.
6MW = 6-minute walk.
IOS = impulse oscillometry.
IC = inspiratory capacity.
IRV = inspiratory reserve volume.
TLC = total lung capacity.
RV = residual volume.
AV = alveolar volume.
KCO = exponential decay constant of the fractional concentration of CO in an apnea time.
Rrs = resistance of the respiratory system.

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Xrs = respiratory system reactance.
HU = Hounsfield units.
QCT = quantitative computed tomography.
FEV_1/FVC = forced expiratory volume of the first second/forced vital capacity.
FEV_3 = forced expiratory volume in 3 seconds.
FEV_6 = forced expiratory volume in 6 seconds.
%WA = percentage of wall area.
RVC = relative volume change.
MRI = magnetic resonance imaging.
PBF = mean pulmonary blood flow.
PBV = pulmonary blood volume.
MTT = mean transit time.
ADC = apparent diffusion coefficient.
PET = positron emission tomography.
R5 = total airway resistance.
R20 = central area track resistance.
XA = reactance area.
Rfreq = resonant frequency.

INTRODUCTION

In middle-income countries, a prevalence of chronic obstructive pulmonary disease (COPD) of 8 to 13% has been described among adults aged 30 to 79 years and older.[1] The Latin American Project for Research on Chronic Obstructive Pulmonary Disease (PLATINO) described a prevalence of COPD of 7.8 to 20.0%, more frequent in men and at older ages, as well as in people with low educational level, low body mass index and exposed mainly to tobacco. Worldwide, there is a wide variation in diagnosis, with 10-95% underdiagnosis and 5-60% overdiagnosis.[2] By 2030, it will be the seventh leading cause of disability-adjusted life years (DALYs) worldwide. Costs attributable to the disease are primarily associated with the number of exacerbations; in the United States, the direct costs of COPD are estimated at $50 billion in direct health care expenditures.[3]

COPD is a complex and heterogeneous condition, characterized by chronic and irreversible obstruction to expiratory airflow, due to the combination of airway remodeling and pulmonary emphysema. The genesis of the disease is influenced by genetic factors, such as hereditary alpha-1 antitrypsin deficiency, matrix metalloprotease deficiencies, childhood disadvantage factors, as well as exposure to occupational, atmospheric or indoor pollutants.[4]

The evaluation and follow-up of COPD is done both by clinical parameters and by respiratory function tests (RFTs). Recently, the improvement in the quality of tomographic imaging and in the quantification of volumetric parameters related to emphysema and airway damage allow a better complementary assessment, which can be used for early diagnosis and follow-up purposes. The present review aims to describe the current status of information related to functional imaging and RFTs, as well as their future prospects for clinical use in the characterization of COPD.

DIAGNOSIS AND FUNCTIONAL ASSESSMENT OF COPD

The current diagnosis of COPD is considered a construct that integrates causes or risk factors, persistent respiratory symptoms and the presence of non-reversible airflow obstruction defined by a ratio < 0.7 between forced expiratory volume and forced vital capacity (FEV_1 and FVC).[5,6] However, these criteria may be modified in the future; several cohorts of patients who do not meet the definition of obstruction show loss of lung function and associated increased morbidity.[7]

While spirometry describes airflow limitation, additional RFTs can be incorporated, such as measurement of: static volumes by plethysmography, diffusing capacity of the lungs for carbon monoxide (DLco), six-minute walk (6MW) and impulse oscillometry (IOS), which can be useful in staging the disease and tailoring medical treatment to the needs of a heterogeneous population. Plethysmography can demonstrate air trapping and pulmonary hyperinflation, manifested by reduced inspiratory capacity (IC) and inspiratory reserve volume (IRV) with increased total lung capacity (TLC) and residual volume (RV). These indicators define pulmonary hyperinflation and air trapping, the loss of elastic recoil and the load to be broken by the respiratory muscles.[8] In addition, it is related to mortality and exacerbations, may be an indicator for volume reduction surgery, especially for IC, and the RV/TLC ratio.[9,10]

In principle, a decreased DLco is an indicator of emphysema and may be due to a fall in alveolar volume (AV), mainly due to obstructive defects and/or emphysema, with a fall in the carbon monoxide transfer coefficient (KCO).[11] A DLco value < 60% is associated with decreased exercise capacity, risk of death regardless of the degree of obstruction, and may represent a small group with precapillary pulmonary hypertension.[12] In smokers without obstruction, a value < 80% predicts an increased risk of developing COPD.

The IOS application provides detailed information on airway properties, estimates respiratory system resistance (Rrs) and respiratory system reactance (Xrs). The findings in COPD consist of an increased Rrs and a decreased Xrs value.[13] These findings are suggestive of small airway obstruction and, more importantly, correlate with the severity of obstruction at this level.

The 6MW is a submaximal exercise test. It is a sign of functional capacity in relation to exercise. It can indirectly show maximal oxygen consumption and is considered more representative of patients' daily activity. A reduced distance is an adequate index of functional disability and increased risk of mortality,[14] although the prediction of hospitalization for exacerbation is unclear.

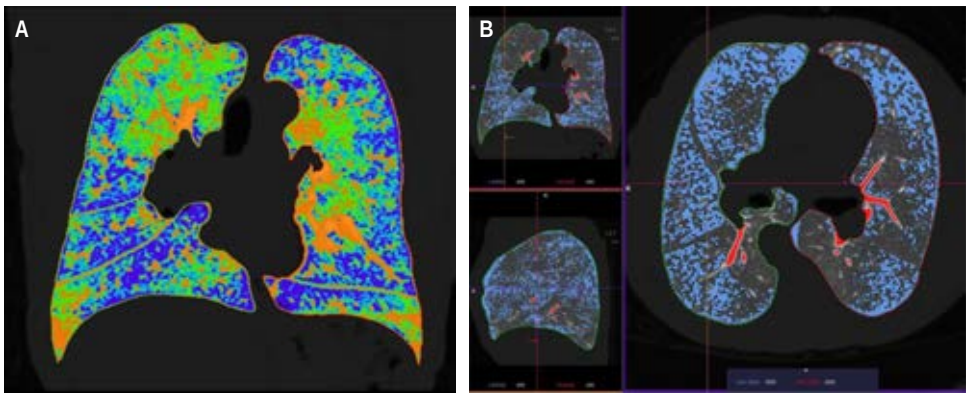

Figure 1:

Representative CT scan of the volumetric evaluation. **A)** The parametric mapping can be seen in coronal plane, where each color corresponds to a voxel with a different percentile, the cut-off point is the 15th percentile. **B)** The evaluation of parametric mapping is observed in multiplanar reconstruction, where all voxels in blue correspond to areas of low attenuation, lower than the cut-off point -950 HU (Hounsfield units).

TOMOGRAPHIC EVALUATION

In 1970 Hounsfield developed computed tomography (CT) for clinical use. Emphysema was described by tomography in the late 1970s and early 1980s. Previously, histologic and postmortem studies were required to evaluate pulmonary structural changes. The introduction of CT made it possible to visualize the thorax and lung structure noninvasively. In 1978, Rosenblum et al. described the areas of low attenuation and average lung density in patients with a clinical diagnosis of COPD.[15]

The need to understand the pathophysiological process of COPD translates into the need to quantify parenchymal and airway damage as a means to closely relate physiological alterations and clinical manifestations. Stereology (spatial interpretation by sections) is the quantification of lung volume by imaging and was initially used in histopathology to be adopted later to quantitative analysis by tomography, to the analysis of normal lung and then expanded to the field of COPD, to provide numerical information of emphysema, and development of a visual stratification system by estimating the number of axial tomography slices, which showed a strong association with airflow obstruction and histological specimens. Subsequently, automated techniques were developed to segment the lung parenchyma and quantify emphysema. The two main techniques initially described used the principle where emphysematous regions are represented by areas of low attenuation: the first method is called tomographic densitometry and the second, percentile densitometry, involves the choice of an average distribution curve, which provides the density in Hounsfield units (HU) under which a percentage of voxels are distributed *(Figure 1)*.[15] The Radiological Society of North America has promoted the standardization of lung densitometry for COPD within the framework of the Quantitative Imaging Biomarkers Alliance® (QIBA®).[16]

Physiopathogenesis and association with imaging

Quantitative histological assessment of the diseased lung, as well as improved lung imaging (such as CT) and a growing understanding of inflammation, cell signaling and cell death, among others, have provided a major step forward in the understanding of COPD. In this context, the determination of lung volumes is a key parameter in pulmonary stereology to properly interpret quantitative damage. Hogg et al. in 1968 provided key physiological data supporting that the main site of increased airway resistance in COPD was the small airways, in the range of 2 mm in diameter,[16] the authors concluded that increased lung resistance could be due to obstruction of the small airways by mucus, narrowing or occlusion by fibrosis, as confirmed by Thurlbeck.[17] The pathogenesis of increased lung volume and pathophysiology of increased small airway resistance includes that related to the cellular inflammatory process and mediated by innate and adaptive immunity. This inflammation persists for several years even after smoking cessation, suggesting self-perpetuating mechanisms.

There is a strong correlation between quantitative assessment of tomographic density and pathologic quantification. The percentage of low attenuation areas by CT are related to the FEV_1/FVC ratio. This shows that smokers with normal spirometry, but with abnormal CT findings, such as emphysema, may have potential to develop airway obstruction in the future, compared to non-smokers.[18] It has been demonstrated with the use of CT for histopathological specimen analysis (microCT) that the number of terminal and transitional bronchioles is reduced by up to 40% in mild to moderate COPD and up to 80% in severe disease. These findings suggest that this airway represents a «silent area» within the lung where damage can accumulate unnoticed.[19] Resistance to small airway airflow is the main site of obstruction in COPD patients and precedes the onset of emphysematous destruction in COPD phenotypes with centrilobulbar

and paraseptal emphysema. Small airways (smaller than 2 mm) cannot be directly visualized using CT scans; therefore, the finding of air trapping, which is seen as decreased lung attenuation on expiratory CT, can be used as an indirect sign of small airway dysfunction in COPD, and can also be quantified volumetrically; this finding is thought to be caused by early collapse of the small airways on exhalation.

Correlation between the extension of emphysema and functional parameters

Visual and subjective assessment of emphysema using CT with contiguous 10 mm thick slices began in 1986; significant correlations were observed between CT visual scores and macroscopic emphysema. Using visual pulmonary assessment, emphysema severity correlates fairly well with physiologic parameters (FEV_1 and FEV_1/FVC) and GOLD stage. The correlation coefficient ranges from 0.67 (for GOLD stage) to -0.74 (for FEV_1/FVC). In particular, the range of the correlation coefficients is similar to the correlations between the extent of emphysema on quantitative CT (QCT) and each physiological parameter (0.62 for GOLD stage and -0.70 for FEV_1/FVC).[16] However, agreement among readers regarding the severity of emphysema on visual assessment tends to be variable, so quantitative CT is preferred for assessing emphysema severity. In addition, CT measurements have been shown to correlate better with macroscopic measurement of emphysema. *Table 1* shows the relationships between tomographic parameters and RFTs.

Regional heterogeneity of emphysema

The basal distribution of emphysema is associated with major alteration of FEV_1, but with less alteration of gas exchange (PaO2) and alveolar-arterial oxygen gradient, compared with the apical distribution of emphysema.[16] Areas of emphysema on CT are more frequently found in the central areas of the lung than in the distal areas, and the extent of central and lower emphysema correlates much more with airflow limitation compared with distal emphysema *(Figure 2)*.

Correlation between airway measurements and functional parameters

Many studies have shown that patients with higher percent wall area (%WA) have lower FEV_1 expressed as a predicted percentage. The %WA has been considered the most commonly employed metric for clinical

Table 1: Application of respiratory function tests in COPD and their relationship with parametric mapping computed tomography.

Test	Clinical outcomes of PFTs	Correlation with CT
Body plethysmography	CI, increased RV/CPT indicate increased dyspnea, risk of death and may be indicative of volume reduction surgery when severe hyperinflation is present	The ITGV and percentage predicted CPT have a positive correlation (R2 0.33) with the percentage of emphysema, with an AUC of 0.79, indicating hyperinflation
Carbon monoxide diffusion	A DLco with values < 60% is associated with decreased exercise capacity and risk of death. Decreased in precapillary pulmonary hypertension. In non-obstructed values < 80% predict a risk of developing COPD	A percentage of predicted decreased KCO and DLco have a positive correlation with the percentage of emphysema especially when greater than 10% with AUC of 0.78
Oscillometry	IOS is more sensitive than spirometry in identifying peripheral airway pathology. In addition, in COPD patients with FEV_1 < 50%, Xrs is a very sensitive indicator of exacerbations and mortality	IOS analysis especially an R5-R20 index > 0.07 kPa has a positive correlation (r2 = 0.599) with small airway disease related to air trapping (OR 2.01) identifying early disease
6 min walk	Reduced distance at 6MW indicates functional disability and increased risk of mortality	The 6-minute walk has a positive correlation with the severity and percentage of emphysema (r = 0.55)
Other spirometry values or indexes	FEV_1/FEV_6 is simple, has good sensitivity, specificity and is a good predictor of exacerbations. FEV_3/FEV_6 values below LLN are associated with poor quality of life, exacerbations and obstruction. Useful for early diagnosis	FEV_1/FEV_6 increased gas trapping and airway wall thickness FEV_3/FEV_6 has a good correlation with small airway disease and emphysema

PFT = pulmonary function tests. AUC = area under the curve. IQ = inspiratory capacity. TLC = total lung capacity. 6MW = 6-minute walk. DLco = diffusing capacity of the lungs for carbon monoxide. COPD = chronic obstructive pulmonary disease. FEV_1 = forced expiratory volume in the first second. FEV_3 = forced expiratory volume at second 3. FEV_6 = forced expiratory volume at second 6. KCO = Korgh's constant. kPa = kilopascals. LLN = lower limit of normal. OR = odds ratio. R5 = total resistances. R20 = central resistances. Xrs = reactance area. ITGV = intrathoracic gas volume. RV = dual volume.

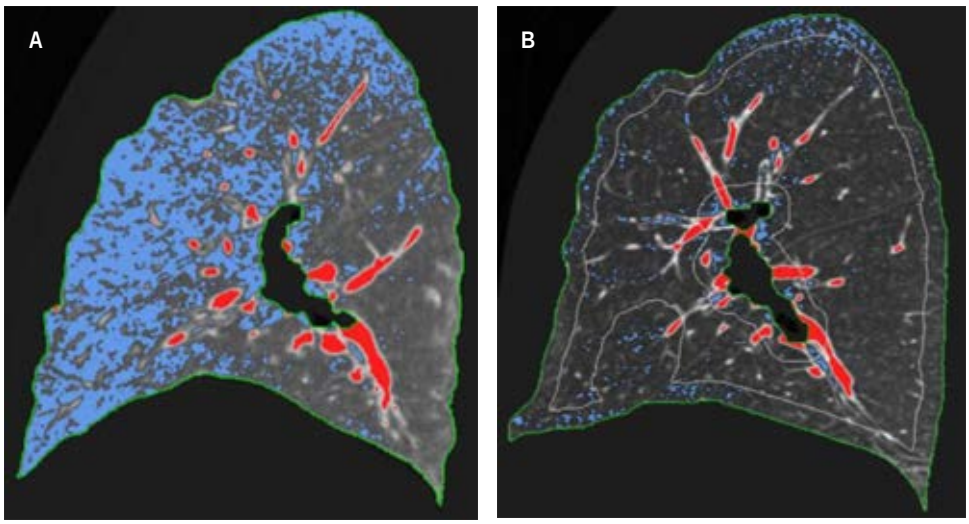

Figure 2:

Sagittal plane parametric mapping. **A)** The predominant distribution of anterior and superior voxels is seen. **B)** Distribution of voxels in blue in the center and periphery of the lung parenchyma; differences in distribution correlate with greater alteration of FEV_1 airflow limitation.

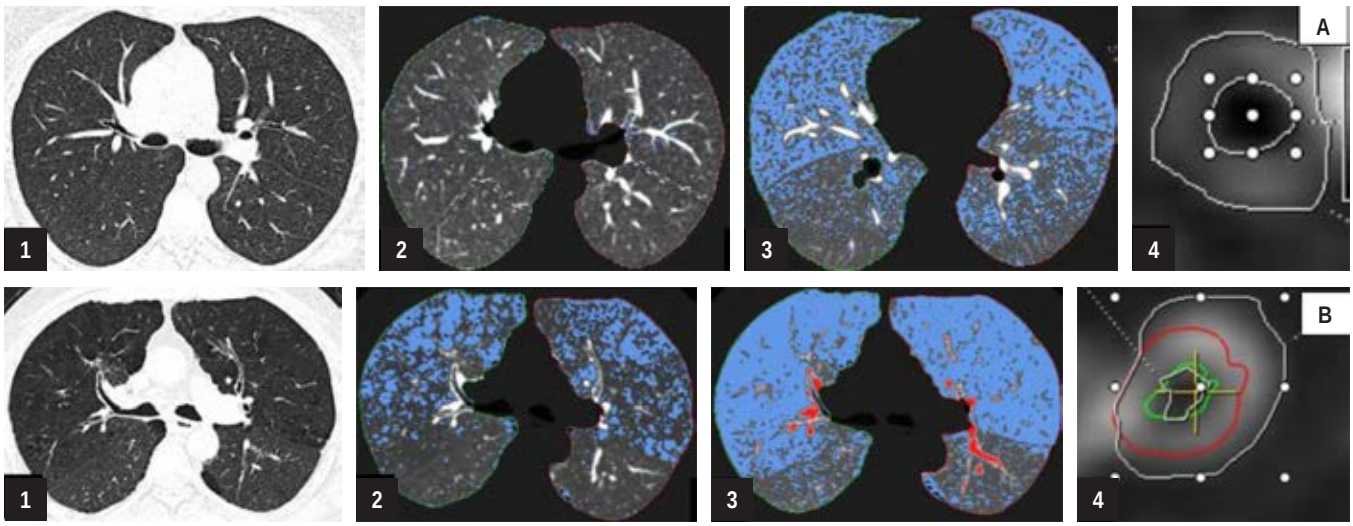

Figure 3: PM CT in patients with COPD and pre COPD secondary to smoking. **A)** CT scan of an ex-smoker patient with dyspnea without spirometric obstruction is shown: CT findings in A1 a normal high resolution CT scan; in A2 the parametric map (PM) shows a volume of 4,482 mL, emphysema index of 3.4%; in A3 PM in expiratory with air trapping of 43.9%, and airway analysis a percentage of wall area (%AP) in A4 of 0.80. His PFTs are characterized by air trapping on body plethysmography (RV/TLC 142% predicted). **B)** Shown is a CT scan of a patient with GOLD 2 COPD due to smoking, dyspnea mMRC2: with centrilobulillar and paraseptal emphysema pattern in B1; PM in B2 with volume of 6,558 mL, emphysema index of 21.9; MPR B3 with air trapping of 56.8% and airway analysis with %AP in B4 of 0.93. His PFRs are characterized by air trapping on plethysmography (RV/TLC 161% predicted, adjusted DLco 57% predicted).

research, and there are modest correlations between it and pulmonary physiologic impairment. Moderate correlations have been described between airway wall measurements and airflow obstruction (FEV_1 and FEV_1 as percent predicted) and stronger correlations are observed when only small airways are analyzed. Relative volume change (RVC) is the parameter that shows that air trapping can be quantified based on the relative lung density in expiration and inspiration, thus expressing the actual degree of air trapping as the difference of the relative percentage of the thresholds in inspiration (-950 HU) and expiration (-860 HU).

Other methods are the air trapping index, which includes the ratio of expiratory to inspiratory lung volume (E/I-LV ratio) and the expiratory to inspiratory ratio of mean lung density (E/I-MLD ratio). E/I-MLD correlates with COPD clinical parameters such as BODE index (r 0.48 - 0.68) and E/I-LV shows a very high correlation with E/I-MLD ($r = 0.95$, $p < 0.001$).[16]

Other evidence has found small airway dysfunction, related to the degree of trapping and the percentage of damage on the parametric map *(Figures 3 and 4)*; small airway dysfunction as assessed by IOS parameters in COPD patients is present in all exacerbations of the disease, particularly in GOLD patients 3-4. Compared to patients with normal IOS parameters, patients with abnormalities in IOS parameters have more respiratory symptoms, more severe airway obstruction, and structural abnormalities on imaging.[15]

OTHER IMAGING METHODS

Magnetic resonance (MR) imaging can provide functional information using perfusion and ventilation techniques in patients with COPD; with the MR perfusion technique, pulmonary blood flow can be quantitatively assessed. Perfusion alterations in COPD often show a low degree of inhomogeneous contrast enhancement, especially in areas of severe emphysema and with decreased peak signal intensity. In patients with severe emphysema, visual assessment of perfusion by 3D MRI shows high concordance with parenchymal destruction. Quantitative analysis confirms decreased perfusion parameters and correlates with worsening FEV_1/FVC and increased CT emphysema index. Perfusion MRI in COPD shows reduced value and heterogeneous change in mean pulmonary blood flow (MBF), pulmonary blood volume (PBV) and mean transit time (MTT) compared to normal volunteers. Other advances in magnetic resonance imaging are those assessed by hyperpolarized gases, such as helium and xenon, which are expressed by ventilatory defects and can be quantified through the apparent diffusion coefficient (ADC) expressed in percentages; these ADC ventilatory defects correlate significantly with lung function tests (FEV_1, FEV_1/FVC and DLco).[16]

Dual-energy computed tomography, another imaging technique for the evaluation of COPD patients, shows that anatomical changes influence alveolar gas exchange and pulmonary blood flow. Pulmonary blood volume, assessed by this technique can be used for pulmonary perfusion assessment as a surrogate for dynamic CT-derived pulmonary blood flow; a simpler protocol that maintains quantitative similarity.

Dynamic perfusion imaging with multidetector CT can also provide regional perfusion. Smokers with subtle findings of centrolobulillar emphysema on CT and normal spirometry have been shown to have increased regional heterogeneity of lung perfusion compared with never-

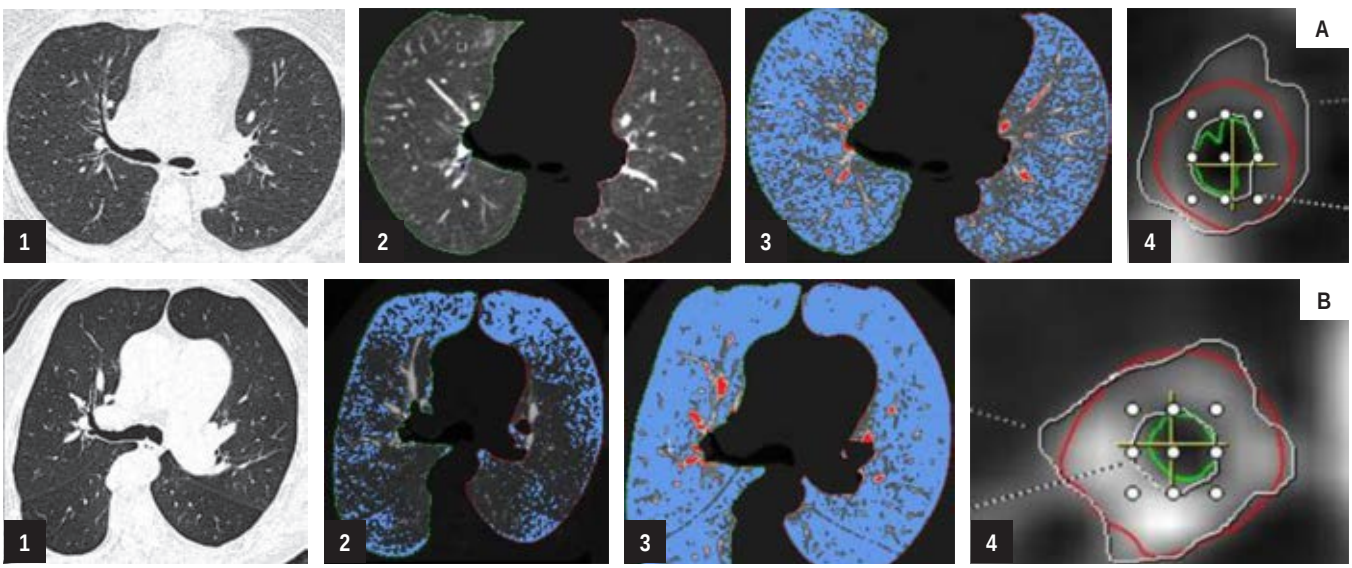

Figure 4: Parametric computed tomography map in patients with wood smoke damage at different stages of the disease. **A)** A CT scan of a patient exposed to wood smoke, chronic bronchitis without spirometric obstruction is shown: with normal high-resolution CT in A1; in A2 PM with volume of 3,960 mL and practically null emphysema index of 0.9%; in A3 MPR expiratory with air trapping of 40.9%, and %AP in A4 of 0.81. His PFTs are characterized by increased small airway resistances on oscillometry (R5Hz 146% pred, R20Hz 130% pred, R5Hz-R20Hz 0.15 KPa L/s). **B)** A CT scan of a COPD GOLD 2 patient exposed to wood smoke, chronic bronchitis is shown: the CT scan demonstrates in B1 mosaic pattern, low attenuation centrilobulillar nodules and an increase in the anteroposterior axis of the rib cage; in B2 PM with volume of 3,973 and emphysema index of 25%; B3 PM significant expiratory air trapping of 75.8% and in B4 %AP of 0.84. Their PFTs are characterized by increased small airway resistances in oscillometry (R5Hz 265% pred, R20Hz 142% pred, R5Hz-R20Hz 0.6 KPa L/s).

smokers and smokers with normal CT imaging. This technique requires a central bolus of high-pressure contrast material and scans a limited axial extent of the lung during a synchronized cardiac scan.

Xenon is a radiopaque gas and its concentration in the alveolar space can be measured as a function of CT image attenuation changes. Due to variability in baseline lung attenuation, between images due to misregistration artifacts and different levels of respiration, accurate measurement of lung ventilation function is limited. Two stable gases, xenon and krypton, with high atomic numbers (54 and 36, respectively) are eligible for dual-energy CT ventilation imaging. For xenon ventilation imaging with dual-energy CT, the patient generally inhales stable xenon at a concentration of 30% (mixture of 30% xenon and 70% oxygen) for 1 min to 1 min and 30 seconds and with the use of a xenon gas inhalation system.

Regional ventilation and perfusion can also be assessed with positron emission tomography (PET), using 13N2 isotope as a gas dissolved in saline. Spatial heterogeneity of lung perfusion has also been described with 13N2-saline PET, and regional heterogeneity in perfusion has been increased in patients with mild COPD compared with healthy controls, after adjusting for regional changes in lung tissue density and ventilation. These results suggest that regional perfusion changes may precede lung parenchymal destruction in COPD. Therefore, this imaging method may serve as an early biomarker.

CONCLUSIONS

There is an adequate correlation of PFT and quantitative assessment by CT, as well as other imaging techniques. This has allowed to broaden the knowledge of the pathophysiological process; its multiple metrics show usefulness for the detection of initial findings in early COPD. Furthermore, CT imaging with parametric mapping is emerging to improve the diagnosis and allow the follow-up of this type of patients, as well as for the implementation of early therapeutic strategies.

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