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Diffusing Capacity for Carbon Monoxide Correlates Best With Tissue Volume From Quantitative CT Scanning Analysis

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BACKGROUND: Quantitative analysis of high-resolution chest CT scan (QCT) is an established method for determining the severity and distribution of lung parenchymal destruction in patients with emphysema. Diffusing capacity of the lung for carbon monoxide (DLCO) is a traditional physiologic measure of emphysema severity and is probably influenced more by destruction of the alveolar capillary bed than by membrane diffusion per se. We reasoned that DLCO should correlate with tissue volume from QCT.

METHODS: A total of 460 patients with upper-lobe-predominant emphysema were enrolled in the study. The mean (SD) of percent predicted values for FEV_1, total lung capacity, and DLCO were 30.6% (8.0%), 129.5% (18.1%), and 6.7% (13.1%), respectively. QCT was performed using custom software; the relationship between DLCO and various metrics from QCT were evaluated using Pearson correlation coefficients.

RESULTS: On average, whole-body plethysmography volumes were higher by 841 mL compared with QCT-calculated total lung volume. However, there was a strong correlation between these measurements ($r = 0.824$, $P < .0001$). DLCO correlated with total lung volume ($r = 0.314$, $P < .0001$), total tissue volume ($r = 0.498$, $P < .0001$), and percentage of lung with low density (−950 Hounsfield units) ($r = -0.337$, $P < .0001$).

CONCLUSIONS: In patients with severe emphysema, DLCO correlates best with total tissue volume, supporting the hypothesis that pulmonary capillary blood volume is the main determinant of DLCO in the human lung. The relationships between DLCO and various anatomic metrics of lung parenchymal destruction from QCT inform our understanding of the relationship between structure and function of the human lung. CHEST 2015; 147(6):1485-1493

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ABBREVIATIONS: CO = carbon monoxide; DLCO = diffusing capacity of the lung for carbon monoxide; Hb = hemoglobin; LAA = low attenuation area; mMRC = modified Medical Research Council; QCT = quantitative analysis of high-resolution chest CT scan; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; Spo_2 = arterial oxygen saturation; TLC = total lung capacity; Vc = pulmonary capillary blood volume; WPB = whole-body plethysmography

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Diffusing capacity of the lung for carbon monoxide (DLCO) is a traditional physiologic measure and is considered to be useful in the evaluation of emphysema severity.[1] DLCO estimates the overall ability of the lung to transport gas into the blood across the alveolar-capillary interface and is determined by structural properties of the lung (eg, accessible alveolar gas volume, diffusion path length, alveolar capillary membrane surface area, and pulmonary capillary blood volume) as well as functional properties (eg, uniformity of ventilation and perfusion, composition of the alveolar gas, and binding properties of hemoglobin [Hb]).[2] Diffusing capacity is estimated by measuring carbon monoxide (CO) uptake from the lung (transfer coefficient) and relating this to the volume of gas in the lung containing CO (effective alveolar volume).

DLCO was originally termed "transfer factor of the lung for CO." The term diffusing capacity itself may be misleading, since gas transport is not exclusively determined by diffusion. The process of gas uptake depends on the two conductance properties: membrane conductance (D_M), which reflects the diffusion properties of the alveolar capillary membrane, and the process of binding of gas and Hb, which can be represented as the product of the gas-Hb chemical reaction rate (θ) and the volume of Hb in alveolar capillary blood (Vc).[2] Since these are conductances in series, their properties are classically represented by the following equation first described by Roughton and Forster (in which D_L is diffusing capacity of the lung)[3]:

$$\frac{1}{D_L}=\frac{1}{D_M}+\frac{1}{\theta\times Vc}$$

Understanding this concept is of exceptional value in certain situations (eg, patients with emphysema), where the destruction of alveolar walls directly affects the integrity of the capillary bed and, thus, reduces DLCO. DLCO is an excellent index of the degree of anatomic emphysema in smokers with airways obstruction.[4] The reduction of DLCO in the patient with emphysema is probably influenced more by loss of alveolar capillary bed ($1/\theta \times Vc$) and reduction of Vc than by membrane diffusion per se ($1/D_M$). Applying this physiologic concept to pathology of patients with emphysema, we can hypothesize that a measurement of the lung parenchyma tissue volume would correlate well with DLCO in a patient with emphysema.

Quantitative analysis of high-resolution chest CT scan (QCT) of the lungs can provide investigators not only with spatial information about larger structures within the lung but also, through densitometry, information about the distribution of lung parenchymal destruction in patients with emphysema, and enables investigators to distinguish lung tissue and airspace. Emphysematous changes can be quantified using CT imaging based on identification of low attenuation areas (LAAs). These areas may reflect parenchymal destruction and enlargement of the airspaces[5,6] The percentage of LAA per total lung volume (LAA%) has been shown to correlate with symptoms in patients with COPD and their pulmonary function.[7-9]

Multiple anatomic metrics derived from the attenuation values on CT scans have been claimed to reflect airway obstruction both in emphysema[1,10,11] and COPD.[12-15] These indexes are shown to have good accuracy[1,16,17] and repeatability.[18] The severity of emphysema in the nonbullous parts of the lungs correlated well with measurements of airflow limitation and diffusing capacity.[19] Correlation between total lung volumes measured by plethysmography and volume estimated by QCT has also been described.[20] A low DLCO correlates highly with a low mean density of lung tissue on lung CT scans and with the degree of anatomic emphysema.[21-23]

Smoking-related lung diseases represent a spectrum of changes to lung structure and function rather than a single disease.[24] Therefore, there is a need for standardization of diagnostic criteria for conditions such as COPD.[25] The potential of QCT scanning to assess both anatomic and physiologic aspects of lung disease makes it a desirable tool for the assessment of smoking-related lung diseases. Our goal was to explore correlations between parameters derived from QCT and DLCO.

Materials and Methods

Patient Selection

The patients reported in this analysis all presented with smoking-related, upper-lobe-predominant emphysema. They were evaluated and considered eligible for participation in one of five studies of bronchoscopic lung-volume reduction by implantation of intrabronchial valves (Spiration, Inc). The studies were carried out in North America, Europe, and South Africa (e-Tables 1, 2). Typical inclusion and exclusion criteria for these studies have been previously published[23,26-29] and are shown in Table 1. All centers received local ethics committee approval prior to enrolling patients in the trial. A total of 460 patients (263 men) with upper-lobe-predominant emphysema were enrolled in the five international clinical trials. The results of one of these studies have been published separately.[28]