Clinical Utility of Computed Tomographic Lung Volumes in Patients with Chronic Obstructive Pulmonary Disease

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Key Words

Chronic obstructive pulmonary disease · Computed tomography · Lung volume measurement · Clinical outcome

Abstract

Background: Published data concerning the utility of computed tomography (CT)-based lung volumes are limited to correlation with lung function. **Objectives:** The aim of this study was to evaluate the clinical utility of the CT expiratory-to-inspiratory lung volume ratio (CT V_{ratio}) by assessing the relationship with clinically relevant outcomes. **Methods:** A total of 75 stable chronic obstructive pulmonary disease (COPD) patients having pulmonary function testing and volumetric CT at full inspiration and expiration were retrospectively evaluated. Inspiratory and expiratory CT lung volumes were measured using in-house software. Correlation of the CT V_{ratio} with patient-centered outcomes, including the modified Medical Research Council (MMRC) dyspnea score, the 6-min walk distance (6MWD), the St. George's Respiratory Questionnaire (SGRQ) score, and multidimensional COPD severity indices, such as the BMI, airflow obstruction, dyspnea, and exercise capacity index (BODE) and age, dyspnea, and airflow obstruction (ADO), were analyzed. **Results:** The CT V_{ratio} correlated significantly with BMI

($r = -0.528$, $p < 0.001$). The CT V_{ratio} was also significantly associated with MMRC dyspnea ($r = 0.387$, $p = 0.001$), 6MWD ($r = -0.459$, $p < 0.001$), and SGRQ ($r = 0.369$, $p = 0.001$) scores. Finally, the CT V_{ratio} had significant correlations with the BODE and ADO multidimensional COPD severity indices ($r = 0.605$, $p < 0.001$; $r = 0.411$, $p < 0.001$). **Conclusion:** The CT V_{ratio} had significant correlations with patient-centered outcomes and multidimensional COPD severity indices.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation as a result of various combinations of small airway disease and emphysema [1]. Expiratory flow limitation and lung hyperinflation are crucial pathophysiological mechanisms in the development of dyspnea, exercise intolerance, and respiratory failure in patients with COPD [2, 3]. The degree of lung hyperinflation is a predictor of functional improvements after bronchodilator therapy and lung volume reduction surgery [4–6]. Furthermore, the inspiratory fraction [inspiratory capacity (IC)/total lung capacity (TLC)], which reflects the functional reserve in patients with COPD, is an important predictor of mortality in patients

with COPD [6]. Therefore, lung volume measurements are useful for the prediction of treatment response and prognosis in patients with COPD.

In contrast to the relative simplicity of spirometric values, a variety of methods have been developed for the measurement of lung volumes, such as body plethysmography, nitrogen washout, gas dilution, and radiologic imaging methods. Plethysmography, though sometimes considered the gold standard, can overestimate lung volume in obstructive lung diseases. Thus, no one method was advocated over the others in the recent American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [7]. Recent advances in computed tomography (CT) allow quantitative assessment of structural changes in COPD. Though many studies have reported significant correlations between quantitative CT metrics and clinically relevant outcomes in patients with COPD [8], CT-based lung volume has not been as rigorously assessed in patients with COPD. The published data concerning the utility of CT-based lung volumes are limited to their correlation with lung function [9–14]. In this study, we hypothesized that the CT expiratory-to-inspiratory lung volume ratio (CT V_{ratio}) would show significant correlations with clinically relevant outcomes in patients with COPD. The aim of this study was to evaluate the clinical utility of the CT V_{ratio} by assessing the relationships with clinically relevant outcomes.

Materials and Methods

Patients

A total of 75 stable COPD patients who were enrolled in the Korean Obstructive Lung Disease (KOLD) cohort at Asan Medical Center between June 2005 and August 2011 were included in this study. The inclusion criteria for the KOLD cohort have been described elsewhere [15]. COPD was diagnosed based on the presence of airflow limitation that was not fully reversible [postbronchodilator 1-second forced expiratory volume (FEV_1)/forced vital capacity (FVC) <70%] and a smoking history (more than 10 pack-years). Baseline clinical data included demographic information, smoking history, chronic bronchitis episodes, pulmonary function tests, chest X-ray, and volumetric CT. The modified Medical Research Council (MMRC) dyspnea scale and St. George's Respiratory Questionnaire (SGRQ) were administered to assess the degree of dyspnea and health-related quality of life (HRQoL). This study was approved by the Asan Medical Center Institutional Review Board (approval No. 2005-0345), and each patient provided written informed consent.

Pulmonary Function Tests

All pulmonary function tests were carried out as recommended by the ATS/ERS. Static lung volumes were measured by body plethysmography (V6200; SensorMedics, or PFDX). For

computations of residual volume (RV) and TLC, the expiratory reserve volume was measured immediately after measurement of the functional residual capacity (FRC), followed by slow inspiratory vital capacity measurements. In accordance with ATS/ERS recommendations [8], at least 3 FRC values within a range of 5% were obtained and the mean value was reported. The RV was calculated as the FRC minus the mean of the technically acceptable expiratory reserve volume; TLC was the sum of the RV and the largest of the technically acceptable inspiratory vital capacity values. The predicted values of lung volumes were calculated from European Community for Steel and Coal (ECSC) data [16].

Computed Tomography

Volumetric CT scans were performed without bronchodilation within a day of pulmonary function tests. All patients were scanned at full inspiration and expiration using 16-slice multi-detector CT scanners. The scanning protocols have been described elsewhere [15, 17]. Before CT scanning, subjects were coached by the technician to hold their breath at full inspiration and full expiration, and technicians were trained to confirm whether full inspiration and expiration could be adequately obtained. Both scans were performed in the supine position. Image data were stored in Digital Imaging and Communications in Medicine (DICOM) format. Acquired data were reconstructed, using a standard algorithm, at thicknesses of 0.625–0.8 mm and increments of 0.625–0.8 mm. The scale of attenuation coefficients ranged from –1,024 to 3,072 Hounsfield units (HU). Using in-house software, images of the entire lung were automatically extracted. The software segmented the lung parenchyma (–1,024 to –400 HU) from the chest wall and the hilum. The trachea, main bronchi, and lobar-to-segmental bronchus were semiautomatically removed. The cutoff level between a normal lung density and a low-attenuation area was defined as –950 HU [18]. The full inspiratory lung volume (V_{insp}), the full expiratory lung volume (V_{exp}), the volume fraction of the lung under –950 HU, and the mean lung density (MLD) were calculated automatically. Airway wall thickness and wall area percentage [defined as wall area/(wall area + lumen area) $\times$ 100] were measured near the origin of 2 segmental bronchi (right apical and left apico-posterior) using a full-width at half-maximum method [19]. All calculations were performed by 3 radiologists based at Asan Medical Center (Seoul, Korea) who were blinded to patient clinical data.

Statistical Analysis

Data are presented as means $\pm$ SD unless otherwise specified. Comparisons between CT lung volumes and body plethysmographic lung volumes were made using paired *t* tests. Relationships between variables were determined using Pearson's correlation coefficient and linear regression analysis. For the evaluation of associations between the CT V_{ratio} and clinical outcomes, multiple regression analysis was also performed after adjusting for age, sex, smoking status, smoking pack-years, CT emphysema extent, and bronchial wall area. Bland-Altman plot analysis was performed for the evaluation of comparative agreement between lung volumes measured by CT and body plethysmography using MedCalc (version 4.2; MedCalc Software, Broekstraat, Belgium). All other statistical analyses were performed using the SPSS statistical package (version 12.0; SPSS Inc., Chicago, Ill., USA), and *p* < 0.05 was considered statistically significant.

Fig. 1. Scatter plot (a) and Bland-Altman plot (b) of TLC and CT V_{insp} .

Table 1. Baseline characteristics of the 75 included patients

Parameter	Mean $\pm$ SD
Post-BD FEV ₁ , % predicted	48.0 $\pm$ 15.2
Post-BD FVC, % predicted	80.4 $\pm$ 13.4
Post-BD FEV ₁ /FVC, %	43.0 $\pm$ 11.3
TLC, % predicted	107.1 $\pm$ 14.5
FRC, % predicted	136.5 $\pm$ 30.6
RV, % predicted	137.8 $\pm$ 41.6
RV/TLC, % predicted	123.7 $\pm$ 24.3
IC/TLC, %	33.2 $\pm$ 8.2
6MWD, m	439 $\pm$ 107
SGRQ total score	39.4 $\pm$ 20.1
BODE score	3.2 $\pm$ 2.3
ADO score	3.2 $\pm$ 1.5

BD = Bronchodilator.

Table 2. Volumetric CT metrics of the 75 included patients

Parameter	Mean $\pm$ SD
$V_{950\text{insp}}$, %	29.8 $\pm$ 15.6
$V_{950\text{exp}}$, %	19.1 $\pm$ 16.1
MLD _{insp}	-895.9 $\pm$ 20.5
MLD _{exp}	-846.0 $\pm$ 46.3
MLD _{exp} /MLD _{insp} , %	94.4 $\pm$ 3.5
Mean wall area, %	67.5 $\pm$ 4.7

$V_{950\text{insp}}$ = Volume fraction of the lung under -950 HU at full inspiration; $V_{950\text{exp}}$ = volume fraction of the lung under -950 HU at full expiration; MLD_{insp} = full inspiratory mean lung density; MLD_{exp} = full expiratory mean lung density.

Results

The baseline clinical characteristics and volumetric CT metrics of the included patients are summarized in tables 1 and 2. Of the 75 COPD patients, 72 (96%) were male. The mean age was 66.6 (SD 7.8) years, the mean smoking history was 42.6 (22.1) pack-years, and the mean BMI was 22.5 (3.4). The mean TLC, FRC, and RV were 6.56 ± 1.15 l, 4.60 ± 1.15 l, and 3.29 ± 1.05 l, respectively. The mean V_{insp} , V_{exp} , and V_{ratio} measured by volumetric CT were 6.19 ± 1.09 l, 4.21 ± 1.20 l, and $67.6 \pm 11.7\%$. There was a strong positive correlation between V_{insp} and TLC ($r = 0.887$, $p < 0.001$) (fig. 1a). However, the mean V_{insp} was significantly less than the mean TLC (mean difference -0.37 l, $p < 0.001$) and the Bland-Altman plot suggested that V_{insp} systematically underestimated TLC (fig. 1b). There were also strong positive correlations of V_{exp} with both FRC ($r = 0.898$, $p < 0.001$) and RV ($r = 0.828$, $p < 0.001$) (fig. 2a, b). The mean V_{exp} was significantly less than the FRC (difference -0.38 l, $p < 0.001$) and larger than the RV (mean difference 0.92 l, $p < 0.001$) (fig. 2c, d).

The CT V_{ratio} was also significantly correlated with FEV₁ (% predicted), FEV₁/FVC (%), TLC (% predicted), FRC (% predicted), RV (% predicted) and diffusing capacity for carbon monoxide (DLCO) (% predicted) ($r = -0.664$, $p < 0.001$; $r = -0.662$, $p < 0.001$; $r = 0.589$, $p < 0.001$; $r = 0.691$, $p < 0.001$; $r = 0.677$, $p < 0.001$, and $r = -0.306$, $p = 0.008$, respectively). The CT V_{ratio} had a moderate correlation with IC/TLC (%) ($r = -0.637$, $p < 0.001$).

Fig. 2. Scatter plots (a, b) and Bland-Altman plots (c, d) of FRC, RV, and CT V_{exp}.

0.001) and RV/TLC (%) ($r = 0.665$, $p < 0.001$) (fig. 3a, b). Among the CT metrics, V_{ratio} had the highest correlation with the expiratory-to-inspiratory MLD ratio ($r = 0.871$, $p < 0.001$).

Table 3 demonstrates the correlations of the CT V_{ratio} and clinically relevant COPD outcomes with those of IC/TLC and RV/TLC. The CT V_{ratio} had significant correlations with BMI ($r = 0.528$, $p < 0.001$). The CT V_{ratio} was also significantly associated with patient-centered outcomes, such as the MMRC dyspnea score, the 6-min walk distance (6MWD), and SGRQ total scores ($r = 0.387$, $p = 0.001$; $r = -0.459$, $p < 0.001$, and $r = 0.369$, $p = 0.001$, respectively). The CT V_{ratio} had significant correlations with the BMI, airflow obstruction, dyspnea, and exercise capacity index (BODE) and age, dyspnea, and airflow ob-

struction (ADO) multidimensional COPD severity indices ($r = 0.605$, $p < 0.001$; $r = 0.411$, $p < 0.001$). Their correlations were comparable to those of IC/TLC and RV/TLC. Multiple linear regression analysis after adjustment for age, sex, smoking status, smoking pack-years, CT emphysema extent, and bronchial wall area showed that the CT V_{ratio} had significant associations with the 6MWD and the BODE index (table 4).

Discussion

With this study, we are the first to report that the CT V_{ratio}, which demonstrates the collapsibility of the lung, correlates significantly with patient-centered outcomes,

Fig. 3. Correlation of the CT V_{ratio} with IC/TLC (a), and RV/TLC (b).

Table 3. Correlation of the CT V_{ratio} , IC/TLC, and RV/TLC with clinical parameters

Parameter	CT V_{ratio} (%)	IC/TLC (%)	RV/TLC (%)
Age (years)	0.176 (0.131)	-0.302 (0.008)	0.348 (<0.001)
BMI, kg/m ²	-0.528 (<0.001)	0.640 (<0.001)	-0.551 (<0.001)
MMRC dyspnea score	0.387 (0.001)	-0.491 (<0.001)	0.511 (<0.001)
Post-BD FEV ₁ (% predicted)	-0.649 (<0.001)	0.737 (<0.001)	-0.791 (<0.001)
6MWD (m)	-0.459 (<0.001)	0.614 (<0.001)	-0.456 (<0.001)
SGRQ total score	0.369 (0.001)	-0.532 (<0.001)	0.498 (<0.001)
BODE score	0.605 (<0.001)	-0.751 (<0.001)	0.735 (<0.001)
ADO score	0.411 (<0.001)	-0.567 (<0.001)	0.633 (<0.001)

Results are presented as r values (p values).

Table 4. Multivariate linear regression analysis of clinical parameters

Parameter	Standardized coefficient (β) ^a	p value
MMRC dyspnea score	0.151	0.190
6MWD (m)	-0.260	0.017
SGRQ total score	0.152	0.196
BODE score	0.361	<0.001
ADO score	0.144	0.082

^a Adjusted for age, sex, smoking status, smoking pack-years, CT emphysema extent ($V_{950insp}$ %), and wall area (%).

including dyspnea, exercise capacity, HRQoL, and multi-dimensional COPD severity indices (BODE and ADO). Furthermore, the correlations with COPD outcomes were comparable to those of IC/TLC and RV/TLC. Thus, we believe that the CT V_{ratio} is of clinical utility for the assessment of COPD patients.

Expiratory flow limitation, air trapping, and hyperinflation are well-known problems in COPD patients. Although spirometry is the gold standard for diagnosis and monitoring of COPD, FEV₁ has limited utility in assessing the response to bronchodilators or predicting patient-centered outcomes [3]. Actually, lung volumes such as

FRC or IC have been shown to correlate better than FEV₁ with patient-centered outcomes such as dyspnea, exercise tolerance, and HRQoL [20–22]. Although, lung volume measurement is not routinely recommended for COPD patients, it is a prerequisite preoperative evaluation tool for severe COPD patients who are considered for lung volume reduction surgery or bronchoscopic lung volume reduction [23, 24].

The three most commonly used methods for lung volume measurements are body plethysmography, helium gas dilution, and nitrogen washout. The gas dilution-washout methods can underestimate lung volumes because they do not measure areas of the lung that contain trapped gas in patients with airflow limitation. In contrast to the gas dilution-washout methods, body plethysmography can overestimate lung volumes due to incomplete equilibration of mouth and alveolar pressure in patients with severe airflow limitation [25]. Therefore, radiographic lung volumes may be more feasible than physiological measurements in COPD patients with a limited ability to cooperate [26]. Although there were a number of earlier efforts to measure lung volumes from chest radiographs, they were less accurate than CT. Three-dimensional volumetric CT could be considered a reliable tool for the evaluation of lung volumes in patients with COPD [10]. In this study, we demonstrated a high correlation between V_{insp} and TLC. Given good correlations, accurate measurement of the absolute lung volume is a major goal. In this study, the V_{insp} systematically underestimated the TLC by 370 ml. Most of this difference must be attributed to the supine position during the CT scan compared to the sitting position during pulmonary function testing. It has been reported that the supine position leads to a reduction of about 500 ml in TLC or a reduction of vital capacity by a mean of 9% [27]. Additionally, the TLC includes the total dead space (trachea and the oral cavity). Taking those differences into account, we believe that the inspiratory CT lung volume accurately represents the TLC. Furthermore, the expiratory CT lung volume also had good correlations with FRC and RV. In a clinical context, hyperinflation implies an abnormal increase in the volume of gas at the end of tidal breathing (FRC or RV). The RV/TLC and the FRC/TLC ratios are commonly used as surrogates for air trapping. Comparing absolute expiratory CT volumes with the RV, an overestimation of about 920 ml was observed. This result shows that expiratory CT was not performed at full expiration. In fact, it is hard for COPD patients to completely exhale to RV during CT scanning.

In addition to lung volumes, volumetric CT can provide quantitative assessment of emphysema, air trapping,

and large airway thickness [15]. Inspiratory and expiratory CT scans can provide a unique signature for the diagnosis of COPD phenotypes and disease progression [28]. In this study, the CT V_{ratio} showed significant correlations with clinically relevant COPD outcomes that were comparable to those of IC/TLC and RV/TLC. Thus, combined assessment of lung volume and disease components of COPD with CT can be valuable decision-making tools in the management of severe COPD patients. A major advantage of measuring the CT V_{ratio} would be its application for unstandardized CT data [14]. It is a robust index for protocol differences compared to MLD and the percentage of low-attenuation area, which are very sensitive to differences in scanning/reconstruction protocols [29, 30]. Another advantage of CT lung volume measurement would be its capacity for lobar lung volume measurement, which is important in assessing the efficacy of lung volume reduction treatments [12]. Furthermore, recent studies showed that CT lung and lobar volume measurements had better reproducibility than body plethysmography in the Endobronchial Valves for Emphysema Palliation Trial (VENT) [31]. Lobar lung volume measurements on both inspiratory and expiratory scans may reveal the heterogeneous severity of air-trapping in each lobe, and it may be useful for the determination of target lobes for lung volume reduction treatments. However, it has limitations for routine evaluation of COPD patients because it is not yet standardized and may not be available in many centers. Besides technical problems such as prolonged breath-holding, the risk of radiation exposure further limits its usefulness. In the future, simultaneous performance of CT lung volume measurements and body plethysmography may be possible. This combined method may provide accurate measurements of lung volume and further physiological insights into lobar heterogeneity in COPD, which may be particularly important for the selection of candidates most likely to benefit from lung volume reduction.

We should mention some limitations in this study. Firstly, although we carefully instructed every patient how to breathe before undergoing the scans, we did not fully evaluate the patients' cooperation, particularly on expiratory scans. This may be one of the reasons for the relatively weaker correlation between expiratory lung volume and RV compared to those between inspiratory lung volume and TLC. Secondly, the threshold of –400 HU for determining the lung parenchyma could be debated. Although several previous studies have adopted this threshold both for inspiratory and for expiratory CT scans [11, 14], a higher threshold has also been reported

[12, 15]. However, we think our study results may be robust, relative to different thresholds, because it has been reported that various higher thresholds (−200 to −500 HU) do not significantly influence correlations with TLC or RV [11].

In conclusion, the CT V_{ratio} shows significant correlations with patient-centered outcomes and multidimensional COPD severity indices. Future longitudinal studies may reveal the clinical utility of the CT V_{ratio} in prediction of the treatment response and other clinical outcomes such as exacerbations and mortality.

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Financial Disclosure and Conflicts of Interest

J.B. Seo was an investigator in a government-sponsored study (2006–2008, Korea Science and Engineering Foundation).

Y.-M. Oh has been an investigator in university-sponsored studies (Asan Institute for Life Science, University of Ulsan College of Medicine) and an industry-sponsored study (MSD Korea and AstraZeneca Korea) and has participated as a speaker at scientific meetings organized and financed by various pharmaceutical companies (Handok, GlaxoSmithKline, AstraZeneca Korea, MSD Korea, and Boehringer Ingelheim) and a magazine company (Korea Doctors' Weekly).

S.-D. Lee serves as a consultant for GlaxoSmithKline and has participated as a speaker at scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, and Boehringer Ingelheim).

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