

Total lung capacity by plethysmography and high-resolution computed tomography in COPD

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Aim: To characterize and compare total lung capacity (TLC) measured by plethysmography with high-resolution computed tomography (HRCT), and to identify variables that predict the difference between the two modalities.

Methods: Fifty-nine consecutive patients referred for the evaluation of COPD were retrospectively reviewed. Patients underwent full pulmonary function testing and HRCT within 3 months. TLC was obtained by plethysmography as per American Thoracic Society/European Respiratory Society standards and by HRCT using custom software on 0.75 and 5 mm thick contiguous slices performed at full inspiration (TLC).

Results: TLC measured by plethysmography correlated with TLC measured by inspiratory HRCT ($r = 0.92$, $P < 0.01$). TLC measured by plethysmography was larger than that determined by inspiratory HRCT in most patients (mean of 6.46 ± 1.28 L and 5.34 ± 1.20 L respectively, $P < 0.05$). TLC measured by both plethysmography and HRCT correlated significantly with indices of airflow obstruction (forced expiratory volume in 1 second/forced vital capacity [FVC] and FVC%), static lung volumes (residual volume, percent predicted [RV%], total lung capacity, percent predicted [TLC%], functional residual capacity, percent predicted [FRC%], and inspiratory capacity, percent predicted), and percent emphysema. TLC by plethysmography and HRCT both demonstrated significant inverse correlations with diffusion impairment. The absolute difference between TLC measured by plethysmography and HRCT increased as RV%, TLC%, and FRC% increased. Gas trapping (RV% and FRC%) independently predicted the difference in TLC between plethysmography and HRCT.

Conclusion: In COPD, TLC by plethysmography can be up to 2 L greater than inspiratory HRCT. Gas trapping independently predicts patients for whom TLC by plethysmography differs significantly from HRCT.

Keywords: lung capacity, plethysmography, high-resolution computed tomography, gas trapping, lung volume measurement errors

Background

Estimation of lung volume is used to help categorize the type, severity, and progression of lung diseases, and their response to therapy.¹ The overestimation of total lung capacity (TLC) by body plethysmography compared with high-resolution computed tomography (HRCT) (or, as some see it, the underestimation by HRCT compared with plethysmography) is well described in the literature.²⁻⁴ The degree to which TLC measured by body plethysmography differs from HRCT in COPD is not understood. This may have significant implications for determining patient eligibility for therapies such as lung volume reduction surgery, characterizing a prospective lung transplant recipient's lung volume dimensions, or assessing the response to treatment.⁵ Our objective was

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to describe the degree to which TLC determination by body plethysmography differs from HRCT. Further, we sought to identify variables that may predict this difference.

Materials and methods

Study patients

A retrospective review was performed on 71 sequential patients referred to our outpatient clinic for the evaluation of COPD between September 2008 and December 2008. Patients who met the following criteria were extracted: (1) obstructive physiology evidenced by forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ≤ 70 and TLC ≤ 80 , (2) no or minimal radiographic abnormalities, or (3) complete pulmonary function tests (PFTs) and HRCT within 3 months.

PFTs

All patients underwent PFTs that were performed on a body plethysmograph (VMax Spectra 22D/62J; Carefusion, Yorba Linda, CA) according to the guidelines of the American Thoracic Society/European Respiratory Society. TLC was obtained as per American Thoracic Society/European Respiratory Society standards.^{6,7} Patients were excluded if they failed to meet criteria for reproducibility, which was defined as the patient demonstrating at least three functional residual capacity (FRC)_{pleth} values that agree within 5% (two patients), or if they failed to perform three to five technically

satisfactory panting maneuvers at frequencies at or around 1 Hertz (two patients).

Chest HRCT

HRCT scans with 0.75 and 5 mm contiguous slices were performed at full inspiration using a 16 or 64 MDCT scanner (Somatom Sensation; Siemens Medical Systems, Erlangen, Germany). Technical parameters included kVp of 100–120 determined by estimation of body mass index. Patients underwent helical computed tomography (CT) of the entire lung at maximum inspiration in the supine position. Patients received breathing instructions by recorded voice commands from the CT scanner. Custom software (Pulmonary Workstation Plus, VIDA Diagnostics, Inc, Coralville, IA) was used to determine total lung volume, tissue volume, and air volume in milliliters, and mean lung density in Hounsfield units (HU) for each patient. All voxels marked as lung parenchyma were analyzed. Percent emphysema was determined as the percentage of voxels below thresholds of -950 and -910 HU. Total volume at full inspiration represents the TLC by HRCT for all analysis (Figure 1). HRCT scans were excluded from analysis for radiographic abnormalities other than emphysema including parenchymal consolidation, pleural effusion, and previous lung volume reduction surgery (LVRS) or transplant surgery (two patients). Patients were also excluded from analysis when the VIDA software was unable to process the scan

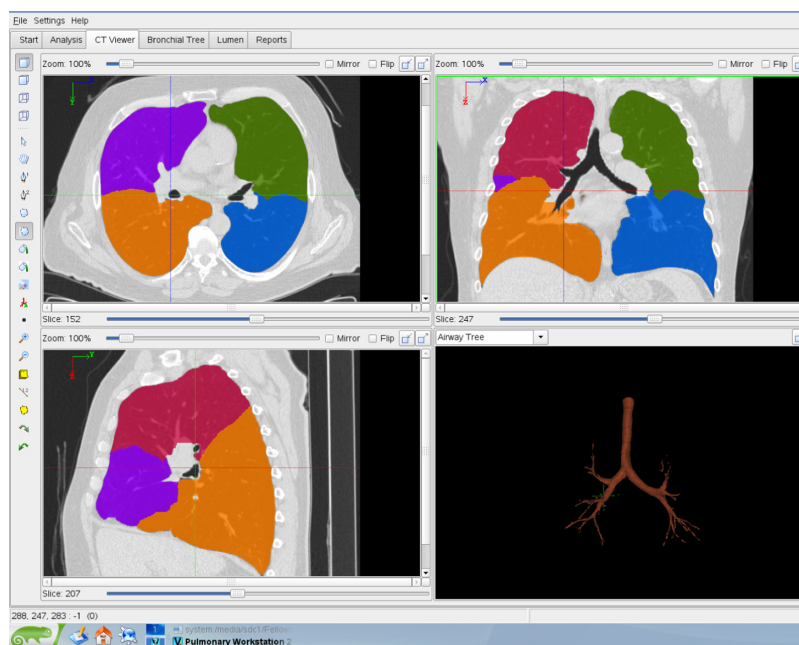


Figure 1 Diagram of the lungs of a 61-year-old man with COPD. The transverse view (top left), coronal view (top right), and sagittal view (bottom left) are at the same anatomical level, as well as three-dimensional rendering of tracheobronchial tree (bottom right).

due to technical difficulties, including failure to identify the tracheobronchial tree (six patients).

Statistical analysis

Student's *t*-test was used for comparison of TLC by plethysmography and HRCT. The Wilcoxon signed rank test was used where normality was not met. Spearman's rank order correlation and Bland–Altman analysis were used for comparison of TLC by plethysmography and HRCT. Multiple linear regressions were used to determine which variables accounted for the ability to predict the difference between TLC measured by plethysmography and HRCT. Data are presented as mean \pm standard deviation unless otherwise indicated.

Results

Demographics, pulmonary function data, and HRCT results obtained from the 59 patients are reported in Tables 1–3 respectively. Pulmonary function testing and HRCT were performed within 3 ± 20 days of each other. The subject population included 18 patients (31%) with Global Initiative for Chronic Obstructive Lung Disease (GOLD) II disease, 22 patients (37%) with GOLD III disease, and 19 patients (32%) with GOLD IV disease.⁸

Total lung volume as measured by plethysmography correlated significantly with that measured by HRCT ($r = 0.92$, $P < 0.01$) (Figure 2). TLC measured by plethysmography (average 6.46 ± 1.28 L) was larger than that determined by inspiratory HRCT (5.34 ± 1.20 L) in most patients ($P < 0.05$). In Bland–Altman analysis, the average of the two measurements is thought to represent the “true value.” As the true value increases the difference between the two modalities also increases (Figure 3). The mean TLC measured by plethysmography was 1.12 L greater than TLC measured by HRCT.

We found FEV₁ to be significantly correlated with percent emphysema and mean lung density, a result which agrees with that reported by Baldi et al.⁹ FEV₁ was not significantly correlated with lung volume measured by plethysmography or HRCT, however, or with the difference between plethysmography and HRCT (Table 4).

Table 1 Demographics in 59 patients with COPD

Variables	Mean	SD or % total
Age (years)	63	9
Male	27	46%
Caucasian	47	80%
BMI	27	6
Pack-years	41	18

Abbreviations: BMI, body mass index; pack-years, packs of tobacco smoked per day \times years as a smoker; SD, standard deviation.

Table 2 Pulmonary function in 59 patients with COPD

Variables	Mean	SD
FEV ₁ /FVC	0.36	0.12
FVC (L)	2.98	0.94
FVC%	85	17
FEV ₁ (L)	1.08	0.52
FEV ₁ %	41	18
FEF 25–75(L)	0.61	0.23
FEF 25%–75%	29	20
RV (L)	3.38	1.0
RV%	164	48
TLC (L)	6.46	1.28
TLC%	115	15
RV/TLC	0.52	0.11
FRC (L)	4.44	1.08
FRC%	146	32
IC (L)	2.02	0.73
IC%	86	22
IC/TLC	0.31	0.09
DLCO/VA	2.49	0.78
DLCO/VA%	50	15

Abbreviations: DLCO/VA, carbon monoxide diffusing capacity corrected for alveolar volume; DLCO/VA%, carbon monoxide diffusing capacity corrected for alveolar volume, percent predicted; FEF 25–75(L), forced expiratory volume during midexpiratory flow; FEF 25%–75%, forced expiratory volume during midexpiratory flow, percent predicted; FEV₁, forced expiratory volume in 1 second; FEV₁%, forced expiratory volume in 1 second, percent predicted; FRC, functional residual capacity; FVC, forced vital capacity; FVC%, forced vital capacity, percent predicted; IC, inspiratory capacity; RV, residual volume; RV%, residual volume, percent predicted; SD, standard deviation; TLC, total lung capacity; TLC%, total lung capacity, percent predicted.

As has been reported by others,^{10–13} there was fair correlation between TLC measured by both plethysmography and HRCT with indices of airflow obstruction (FEV₁/FVC and FVC%), static lung volumes (residual volume, percent predicted [RV%], total lung capacity, percent predicted [TLC%], functional residual capacity, percent predicted [FRC%], inspiratory capacity, percent predicted), and percent emphysema. Both TLC by plethysmography and HRCT showed weak but significant inverse correlations with diffusion impairment (Table 5).

The difference between TLC as measured by plethysmography and HRCT correlated significantly with static

Table 3 HRCT in 59 patients with COPD

Variables	Mean	SD
HRCT total volume (L)	6.05	1.26
HRCT tissue volume (L)	0.71	0.16
HRCT air volume (L)	5.34	1.20
HRCT density (HU)	–873.15	29.47
Emphysema less than –950 (%)	27.74	14.9
Emphysema less than –910 (%)	50.54	16.23

Abbreviations: Emphysema less than –950, percent of voxels with Hounsfield units less than –950; emphysema less than –910, percent of voxels with Hounsfield units less than –910; HRCT, high-resolution computed tomography; HU, Hounsfield units; SD, standard deviation.

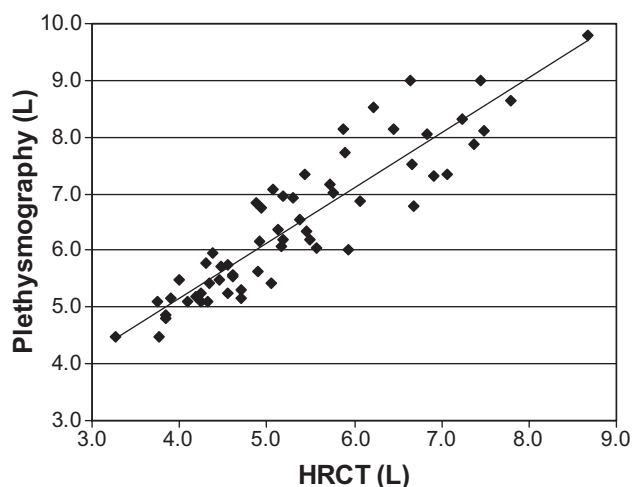


Figure 2 Correlation between inspiratory lung volume by HRCT and TLC derived from PFT results.

Notes: $r = 0.92$, $P < 0.01$.

Abbreviations: HRCT, high-resolution computed tomography; TLC, total lung capacity.

lung volumes (RV%, TLC%, and FRC%) (Table 5, Figures 4 and 5). In patients with more severe air trapping and hyperinflation, the difference between TLC measured by plethysmography and that determined by HRCT increased. Using multiple linear regressions, RV% and FRC% independently predicted the differences between TLC measured by plethysmography and HRCT (Table 6).

Discussion

Thoracic gas volume (TGV) can be measured in several different ways. In patients with COPD, body plethysmography is usually preferred to nitrogen washout and gas dilution techniques because it is argued that the latter methods are

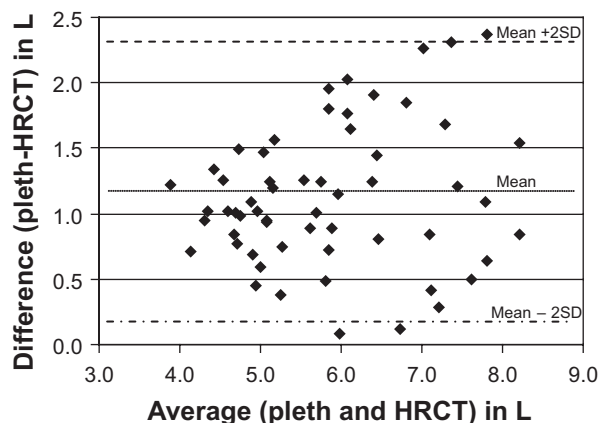


Figure 3 This plot of the difference between the methods against their mean illustrates the relationship between the measurement error and the true value. Total lung capacity measured by plethysmography is 1.12 L greater than total lung capacity measured by HRCT. Greater variation from the mean is seen at higher lung volumes, suggesting measurement error is greater at higher lung volumes.

Abbreviations: HRCT, high-resolution computed tomography; pleth, plethysmography.

Table 4 Comparison of FEV₁% with plethysmography and HRCT

Variables	FEV ₁ %	
	r	P
Plethysmography	-0.25	0.06
Plethysmography-HRCT	0.05	0.71
HRCT total (L)	-0.22	0.10
HRCT tissue (L)	0.26	0.05
HRCT air (L)	-0.29	0.03
HRCT density (HU)	0.48	0.00
Emphysema less than -950 (%)	-0.43	0.00
Emphysema less than -910 (%)	-0.49	0.00

Abbreviations: FEV₁, forced expiratory volume in 1 second; RV, residual volume; FRC, functional residual capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; TLC, total lung capacity.

unable to measure poorly ventilated or unventilated areas of the lung.¹⁴⁻¹⁶ While body plethysmography readily measures trapped air not in communication with the airways, it is not without its own inherent errors, particularly in patients with increased airway resistance. TGV is calculated using Boyle’s law which states that pressure and volume are inversely proportional when temperature is constant. Within the body box, pressure at the mouth may not reflect true pressure in the alveoli if airway resistance increases.^{17,18} If alveolar pressure is underestimated, thoracic gas volume will be overestimated. Rodenstein et al demonstrated this error in the measurement of lung volumes by plethysmography when airflow obstruction occurs, and found thoracic gas volume measured from pressure swings at the mouth (TGV_m) to be 1 or more liters greater than thoracic gas volume measured from pressure swings in the esophagus (TGV_{es}), an indirect measurement of pleural pressure.¹⁹ The authors went on to qualify this overestimation of TGV in the setting of airflow obstruction as being dependent on panting frequency.²⁰ TGV_m was 1 L greater than TGV_{es} at panting frequencies of 2 Hz in asthmatics, while no difference was seen in those without asthma. At higher frequencies, the discrepancy further increased in asthmatics, again with no difference in those without asthma. At lower panting frequencies, no difference was found between the two groups.²¹ This relationship between panting frequency and the overestimation of lung volume by plethysmography has also been described in patients with COPD.^{22,23}

HRCT is an important method for routine testing for COPD. With dedicated post-processing software, rapid and reproducible estimates of tissue and air volume, mean lung density, percent emphysema, and airway anatomy are now available.^{24,25} Standardized computer-generated HRCT instructions have improved reproducibility and accuracy.^{26,27}

Table 5 Correlation coefficients for plethysmography, HRCT, and the difference between plethysmography and HRCT

Variables	Plethysmography		HRCT		Plethysmography–HRCT	
	r	P	r	P	r	P
FEV ₁ /FVC	−0.39	0.00	−0.35	0.01	0.02	0.88
FVC (L)	0.58	0.00	0.66	0.00	0.03	0.84
FVC%	0.06	0.65	0.02	0.87	0.11	0.40
FEV ₁ (L)	0.06	0.63	0.14	0.28	0.04	0.77
FEV ₁ %	−0.25	0.06	−0.22	0.10	0.05	0.71
FEF 25–75 (L)	0.09	0.57	0.08	0.69	0.07	0.80
FEF 25%–75%	−0.30	0.05	−0.27	0.06	0.12	0.39
RV (L)	0.69	0.00	0.54	0.00	0.32	0.02
RV%	0.44	0.00	0.28	0.03	0.29	0.03
TLC (L)	–	–	0.90	0.00	0.31	0.02
TLC%	0.56	0.00	0.34	0.00	0.39	0.00
RV/TLC	0.07	0.60	−0.06	0.67	0.16	0.21
FRC (L)	0.85	0.00	0.74	0.00	0.29	0.03
FRC%	0.48	0.00	0.33	0.01	0.27	0.04
IC (L)	0.38	0.00	0.43	0.00	0.04	0.78
IC%	−0.02	0.87	−0.06	0.67	0.07	0.60
IC/TLC	−0.13	0.33	−0.05	0.72	−0.07	0.61
DLCO/VA	−0.42	0.00	−0.35	0.01	−0.06	0.63
DLCO/VA%	−0.42	0.00	−0.35	0.01	−0.05	0.71
HRCT total (L)	0.90	0.00	–	–	−0.06	0.64
HRCT tissue (L)	0.39	0.00	0.52	0.00	0.10	0.43
HRCT air (L)	0.92	0.00	0.98	0.00	−0.08	0.56
HRCT density (HU)	−0.44	0.00	−0.39	0.00	0.20	0.13
% emphysema less than −950	0.43	0.00	0.41	0.00	−0.18	0.18
% emphysema less than −910	0.49	0.00	0.44	0.00	−0.15	0.26

Abbreviations: DLCO/VA, carbon monoxide diffusing capacity corrected for alveolar volume; DLCO/VA%, carbon monoxide diffusing capacity corrected for alveolar volume, percent predicted; emphysema less than −950, percent of voxels with Hounsfield units less than −950; emphysema less than −910, percent of voxels with Hounsfield units less than −910; FEF 25–75(L), forced expiratory volume during midexpiratory flow; FEF 25%–75%, forced expiratory volume during midexpiratory flow, percent predicted; FEV₁, forced expiratory volume in 1 second; FEV₁%, forced expiratory volume in 1 second, percent predicted; FRC, functional residual capacity; FVC, forced vital capacity; FVC%, forced vital capacity, percent predicted; HRCT, high-resolution computed tomography; HU, Hounsfield units; IC, inspiratory capacity; RV, residual volume; RV%, residual volume, percent predicted; TLC, total lung capacity; TLC%, total lung capacity, percent predicted.

Lung volume measurement by HRCT remains fraught with predictable and unpredictable errors.²⁸ Supine positioning during HRCT results in a reduction in the size of the various subdivisions of the lung.^{29–32} In normal subjects, vital capacity (VC) falls less than 10% when passing from the upright to the supine position,^{33,34} but a reduction of up to 25% has been described in patients with diaphragm dysfunction and respiratory muscle weakness, conditions commonly seen in patients with COPD.³⁵ However, postural changes in VC in patients with COPD have not been well described. Unpredictable errors in the measurement of lung volumes by HRCT include difficulty with maximum inspiratory maneuvers and breath-holding techniques during scanning.³⁶ Using spirometric gating, patients with severe airflow obstruction have not been shown to reproducibly achieve maximum inspiratory volumes during HRCT.³⁷

In similar patient populations, previous authors have shown strong correlations between TLC measured by plethysmography and HRCT (Zaporozhan et al, Coxson et al, and Gierada

et al reported $r = 0.90, 0.88,$ and $0.87,$ respectively).^{2–4} Given what we know about the limitations of plethysmography and HRCT in COPD, we expected to find a relationship between severity of airflow obstruction and the differences in the measurement of TLC between plethysmography and HRCT. If TLC by plethysmography is potentially overestimated in the setting of increased airway resistance, we postulated that as FEV₁ decreased there would be greater differences between TLC measured by plethysmography and HRCT. We further hypothesized that increased airways resistance and subsequent air trapping and hyperinflation³⁸ would be associated with the overestimation of lung volumes by plethysmography. A recent paper by O'Donnell et al compared lung volumes by plethysmography and helium dilution with HRCT in COPD,³⁹ with plethysmographic TLC found to be significantly greater than HRCT values, and plethysmographic overestimation of TLC reported to be greatest among subjects with FEV₁ < 30% of predicted. This was not found to be the case in the current study as differences between TLC measured by

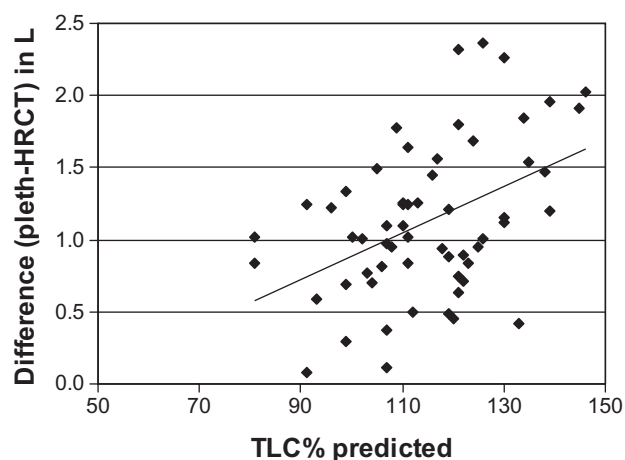


Figure 4 Relationship between TLC% predicted and difference between lung volumes determined by plethysmography (pleth) and HRCT.

Notes: $r = 0.39$, $P < 0.01$.

Abbreviations: HRCT, high-resolution computed tomography; TLC%, total lung capacity, percent.

plethysmography and HRCT did not change across GOLD stages. This relationship between airflow obstruction and the plethysmographic overestimation of TLC may not have been seen because the current study's population included a range of FEV₁ from normal to very severe, and may not be powered sufficiently for subgroup analysis among patients with very severe airflow obstruction. O'Donnell et al collected data from subjects at three hospitals where HRCT and plethysmographic technique may not have been standardized. Patients recruited from one of the hospitals undergoing evaluation for LVRS had substantially lower average FEV₁ than those from the other two hospitals. Subtle differences in HRCT and plethysmographic technique at this hospital may have driven

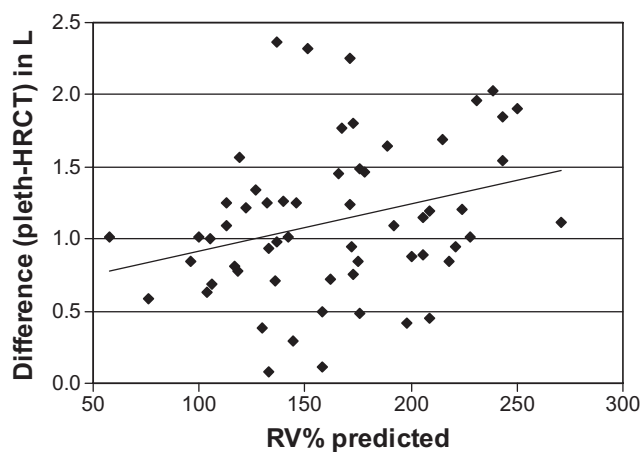


Figure 5 Relationship between RV% predicted and difference between lung volumes determined by plethysmography (pleth) and HRCT.

Notes: $r = 0.29$, $P < 0.01$.

Abbreviations: HRCT, high-resolution computed tomography; RV%, residual volume, percent.

Table 6 Multiple linear regressions

Variables	Plethysmography-HRCT	
	t	P
RV%	-2.14	0.04
TLC%	-0.88	0.39
RV/TLC	0.15	0.88
FRC%	2.33	0.03

Abbreviations: FRC%, functional residual capacity, percent predicted; HRCT, high-resolution computed tomography; RV, residual volume; RV% residual volume, percent predicted; TLC, total lung capacity; TLC%, total lung capacity, percent predicted.

the relationship between airflow obstruction and the overestimation of plethysmographic TLC. Our data were collected at a single center and our methodology was standardized for all patients. No mention was made by O'Donnell et al as to the effect of hyperinflation and air trapping on lung volume determination. Our data suggest that more significant air trapping (RV% and FRC%) and hyperinflation (TLC%) is present in the COPD patients with the greatest difference in TLC measured by plethysmography and HRCT.

Limitations in our study include lack of spirometric gating during image acquisition with HRCT. Sub-maximal inspiratory maneuvers would have resulted in an underestimation of TLC by HRCT compared to plethysmography. Another limitation of our study is that the pulmonary function tests were not necessarily performed on the same day as the HRCT, weakening the correlation between these modalities.

Understanding the variability with which TLC by plethysmography differs from HRCT has important implications in the evaluation of patients with COPD. Global and regional measurements of lung volumes can be important in identifying patients who are most likely to benefit from LVRS.⁴⁰ Similarly, precise volume determination is necessary to accurately identify suitable donor and recipient lungs for transplantation.⁵ Finally, the ability to precisely measure lung volume may be central to determining the importance of hyperinflation in COPD, and the impact of therapies geared to reducing end-expiratory lung volumes.

Conclusion

Total lung capacity measured by plethysmography is larger than that determined by HRCT in COPD. The degree to which TLC measured by plethysmography differs from that determined by HRCT is correlated with air trapping and hyperinflation. RV% and FRC% predict the difference between TLC determined by plethysmography and HRCT.

The method used to obtain TLC in severely hyperinflated patients needs to be considered when precise measurements are required for clinical decision making.

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