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Quantification of Single-Breath Underestimation of Lung Volume in Emphysema

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Abstract

The extent to which a single breath measurement represents available gas dilutional as well as compressible thoracic volume in emphysema patients has not been quantified. We therefore measured single breath (TLC_{SB}) and rebreath helium dilution (TLC_{RB}), and plethysmographic lung volume (TLC_{pleth}), in fifty-five outpatients with clinical and radiographic emphysema, and in twenty-one normal controls. Among emphysema patients, TLC_{SB} increasingly underestimated both TLC_{pleth} and TLC_{RB} as $FEV_1\%$ predicted decreased (p for interaction = 0.001 for both) by a mean of 1.7 liters for TLC_{RB} ($p < 0.001$) and 2.2 liters for TLC_{pleth} ($p < 0.001$). In contrast, TLC_{RB} underestimated TLC_{pleth} by a mean of 0.5 liters ($p < 0.001$) regardless of $FEV_1\%$ (p for interaction = 0.25). TLC_{SB} , TLC_{RB} , and TLC_{pleth} showed strong agreement among normal subjects. We conclude that TLC_{SB} underestimates available gas dilutional and compressible lung volume as physiologic emphysema severity increases. In contrast, TLC_{RB} and TLC_{pleth} show closer agreement which is unaffected by physiologic emphysema severity.

Keywords

Lung Volume Measurements; Pulmonary Function Tests; Emphysema

1. Introduction

In patients with normal airway function, a 10-second single breath inert gas dilution alveolar volume measurement reflects communicating volume of the lung at total lung capacity (TLC) and correlates with multi-breath TLC measurements (Roberts et al. 1990; Punjabi et al. 1998). Measurement of single breath lung capacity has been proposed as a potentially rapid and cost saving methodology to replace multiple-breath methods (Mitchell et al. 1968; Teculescu 1974; Punjabi et al. 1998) and change in single breath lung volume has been utilized as a measure of functional alveolar volume following lung volume reduction surgery in patients with emphysema (Homan et al. 2001). Utilization of measured alveolar volume obtained via

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COMPETING INTERESTS

None

single breath inert gas dilution remains the standard pulmonary function technique to derive diffusing capacity for carbon monoxide ($DLCO_{SB}$) in patients with and without airway obstruction (Macintyre et al. 2005).

In fact, data remain inconclusive regarding the extent to which single breath TLC is a representative measure of available gas dilutional total lung capacity in patients with well-defined emphysema (West et al. 1987). TLC_{SB} was found to be comparable to TLC measured by multi-breath measures in patients with airflow obstruction in one study of patients described as having COPD with a severe obstructive ventilatory defect (Mitchell et al. 1968); another study found that a breath-hold alveolar volume measurement in patients described as having emphysema, or chronic asthma with lung hyperinflation, was similar to that in normal subjects (Pecora et al. 1968). In contrast, other studies (Teculescu 1974; Roberts et al. 1990; Punjabi et al. 1998) have found that patients with expiratory airflow obstruction show reduced ratios of single breath to multi-breath lung volume measurements.

While current American Thoracic Society/European Respiratory Society guidelines caution against interpreting TLC from single breath measurements in the presence of severe airflow obstruction (Pellegrino et al. 2005), no data exist which in fact quantify the extent to which TLC_{SB} reflects concomitantly measured available gas dilutional and gas compressible thoracic volume in patients with emphysema according to the degree of physiologic disease severity. The aim of the current study was to perform such quantification.

2. Methods

2.1 Subjects

All outpatients aged 18 years of age and older referred to the Columbia University Medical Center Pulmonary Diagnostic Unit between January 18, 2006 and February 13, 2008 for full pulmonary function evaluation with a diagnosis of emphysema were considered eligible. Nonsmokers without a history of cardiorespiratory disorders were recruited from hospital staff as controls. The study was approved by the Columbia University Medical Center Institutional Review Board; all subjects signed informed consent prior to testing.

A diagnosis of emphysema was made if a patient fulfilled all of the following criteria: the presence of an obstructive ventilatory defect defined as an $FEV_1/FVC < 5^{\text{th}}$ percentile of the predicted value (Crapo et al. 1981; Pellegrino et al. 2005), a clinical diagnosis by a board certified pulmonologist, and radiographic criteria including the presence of low attenuation areas on chest computerized tomographic (CT) scanning (Goddard et al. 1982).

2.2 Pulmonary Function Testing

Pulmonary function testing was performed in the following order: spirometry, body plethysmography, and single breath (TLC_{SB}) and rebreathe (TLC_{RB}) thoracic volume measurements. The sequence of TLC_{SB} and TLC_{RB} was randomized.

Spirometry and body plethysmography were performed using a V6200 Series Autobox (Sensormedics, Yorba Linda, CA) using ATS/ERS recommendations (Miller et al. 2005; Wanger et al. 2005). Functional residual capacity (FRC_{pleth}) was measured while panting at a frequency of 0.5–1.0 Hz. At least 2 technically satisfactory maneuvers were performed, followed by a linked inspiratory capacity (IC) maneuver, and slow vital capacity maneuver. FRC was reported as the mean of the satisfactory measurements. Plethysmographic volume (TLC_{pleth}) was calculated as $FRC_{\text{pleth}} + IC$, and reported in liters at BTPS.

Participants then underwent single breath (TLC_{SB}) and rebreathe (TLC_{RB}) total lung capacity measurements using the MasterScreen PFT system (Jaeger, VIASYS Healthcare, Hoechberg,

Germany, CD-version JLAB 5.10.0.65) using automated procedures (Stam et al. 1998). Single breath alveolar volume was calculated as:

$$\frac{FI_{He}}{FA_{He}} \times (V_I - V_{D,system})$$

where FI_{He} and FA_{He} represent initial and final He concentrations, respectively; V_I represents the inspired volume; and $V_{D,system}$ represents the dead space volume of the system, expressed as BTPS. TLC_{SB} was calculated as this alveolar volume plus estimated anatomic dead space volume, to optimize comparability with TLC obtained from rebreath and plethysmographic measurements. We accepted only single breath data for which the inspiratory vital capacity was at least 90% of the best vital capacity during all testing. To determine TLC_{RB} , participants were maintained on the breathing circuit, with carbon dioxide kept constant by soda lime absorption; oxygen concentration was maintained between 20% and 22%. Participants breathed at normal ventilation until equilibration, determined by a stable helium wash-in curve and functional residual capacity (Brown et al. 1998), then inhaled to TLC from FRC. FRC_{RB} was calculated as FRC minus dead space of valve and mouthpiece, converted to BTPS (Brown et al. 1998; Wanger et al. 2005). TLC_{RB} was calculated as $FRC_{RB} + IC$. Anatomic dead space was not subtracted from the calculation. Most emphysema patients underwent one TLC_{SB} and one TLC_{RB} maneuver; 9 subjects underwent 2 TLC_{RB} maneuvers. The reported FRC_{RB} was the averaged value. A full description of the lung volume measurement methodology is in the on-line data supplement (ODS).

2.3 Statistical Analysis

Continuous data were summarized by means and standard deviation; categorical data by frequencies and percentages. We used Pearson correlation coefficients and scatterplots to examine the linear relationships between lung volume measurements. We examined agreement between lung volume measurements by calculating the mean differences between volumes and their corresponding 95% limits of agreement (± 1.96 standard deviations) (Bland et al. 1986), with smaller mean differences and narrower limits of agreement indicating greater agreement between measures. “Difference versus mean” plots (Bland-Altman plots) were used to check the assumptions of the limits of agreement. We compared mean differences within groups using Wilcoxon signed rank tests and between groups using Wilcoxon ranks sum tests. We used multivariate linear regression (adjusting for age, gender, height, and BMI) with a multiplicative interaction term between $FEV_1\%$ (or residual volume) and alveolar volume to test whether the degree of airway obstruction (measured by $FEV_1\%$ predicted) and residual hyperinflation modified the relationship between lung volumes. P values for interactions are from Wald tests. There were no missing data. Statistical analyses were performed using SAS 9.1 (Cary, NC).

3. Results

Three hundred and thirty two patients with emphysema were eligible for enrollment during the initial study period. Of these, 66 provided informed consent and were studied. Of these studied patients, we excluded 5 who were unable to reliably perform a single breath maneuver, 3 with $FEV_1/FVC \geq 5^{th}$ percentile, 3 patients for procedural violation, and 4 for data loss. Details for the 263 un-enrolled patients for the initial study period are available in the online data supplement. We added an additional 4 emphysema patients studied between November, 2007 and February, 2008 for a total of 55 emphysema patients. Twenty-one normal volunteers were studied as controls.

Complete demographic and physiologic data for the emphysema patients and controls are displayed in Table 1 and Table 2. Emphysema was generally severe, with a mean $\pm$ SD

FEV₁ of $35 \pm 13\%$, and mean FEV₁/FVC of $39 \pm 11\%$; 86% met criteria for GOLD stage III or IV (Rabe et al. 2007).

For the emphysema patients, time to complete the rebreath maneuver ranged between 2.5 and 7 minutes. All participants were able to reach equilibration. Mean TLC_{pleth} variance for FRC measurements was 0.007 liters among all subjects. For the 9 patients who had 2 TLC_{RB} trials, mean variance for FRC was 0.04 liters.

Among emphysema patients, all pairings of measured alveolar volumes were strongly correlated (Fig. 1A–Fig. 1C: $r \geq 0.62$). Despite these strong correlations, however, TLC_{SB} significantly underestimated TLC_{pleth} (Table 3; mean difference -2.2 liters, 95% limits of agreement -4.5 to 0.0 liters, $p < 0.001$) and TLC_{RB} (mean difference -1.7 liters, 95% limits of agreement -4.0 to 0.5 liters, $p < 0.001$). TLC_{RB} also significantly underestimated TLC_{pleth}, but to a much lesser degree (mean difference -0.5 liters, 95% limits of agreement -2.2 to 1.2 , $p < 0.001$). FRC_{RB} showed a strong correlation with FRC_{pleth} (Fig. 1D; $r = 0.72$, $p < 0.001$), although with wide limits of agreement (mean difference -0.6 , 95% limits of agreement -2.3 to 1.1 , $p = 0.001$). Lung volume pairings were not significantly different among normal subjects except for TLC_{SB} which underestimated TLC_{RB} (mean difference -0.2 liters, 95% limits of agreement -0.8 to 0.4 , $p = 0.008$). Agreement of paired lung volumes for emphysema patients was less than that for normal subjects ($p < 0.001$ for all pairings, Table 3).

Fig. 1 and Fig. 2 show greater disagreement between TLC_{SB} and TLC_{RB} and between TLC_{SB} and TLC_{pleth} at higher lung volumes. In contrast, TLC_{RB} and TLC_{pleth} agreement was largely independent of lung volume. Fig. 3 and Supplemental Table 1 show that the agreement between lung volumes varies by the degree of airway obstruction (as represented by FEV₁% predicted). Among emphysema patients, lower FEV₁% was associated with greater disagreement between TLC_{SB} and TLC_{pleth} (p for interaction = 0.001) and TLC_{SB} and TLC_{RB} (p for interaction = 0.001), but not for TLC_{RB} and TLC_{pleth} (p for interaction = 0.25). Among normals, agreement between lung volumes did not vary by FEV₁% (p for interaction > 0.25 for all).

The order of gas dilution measurement did not significantly affect lung volume relationships (data not shown).

4. Discussion

The current data demonstrate two novel findings regarding measurement of thoracic volume in patients with well-defined emphysema: (1) alveolar volume obtained using a 10 second single breath-hold helium dilution maneuver significantly and, in general, severely underestimates *both* recruitable gas dilutional volume *and* gas compressible volume in proportion to the severity of expiratory airflow obstruction; (2) conversely, most of plethysmographically measured thoracic volume in such patients in fact reflects recruitable gas dilutional lung volume, irrespective of the severity of measured airflow obstruction.

Single breath lung volume measurement has long been proposed as a representative measure of alveolar volume in patients with emphysema and COPD, even in the presence of a severe obstructive ventilatory defect (Mitchell et al. 1968; Pecora et al. 1968; Punjabi et al. 1998; Homan et al. 2001). However, gas dilution techniques measure only accessible communicating volume; slowly ventilating units may thus underestimate lung volume using single breath compared with multi-breath measures. Multi-breath measurement itself may underestimate alveolar volume of poorly ventilated units (Kendrick 1996). Plethysmographic measurements of lung volume, in contrast, may include non-communicating compressible gas within the thorax (Kendrick 1996), and may overestimate volume in subjects with high airways resistance

and expiratory airflow obstruction (Brown et al. 1978; Rodenstein et al. 1982b). The current findings do not define to what extent the small degree of measured discrepancy between TLC_{RB} and TLC_{pleth} represents inability of plethysmography to reflect regions of lung with long time constants (Brown et al. 1998), or overestimation of thoracic gas volume using mouth occlusion pressure changes in the presence of airflow obstruction (Brown et al. 1978; Rodenstein et al. 1982a; Brown et al. 1984). The current data provide documentation to the clinician that TLC_{pleth} reflects to a great extent available gas dilutional thoracic volume even in patients with severe emphysema by pulmonary function and GOLD staging criteria (Rodenstein et al. 1982a; Pare et al. 1983; Andersson et al. 1988).

The rebreathe method of helium gas dilution utilized here allows patients to breathe at their normal alveolar ventilation pattern, and whereas concerns regarding the work of breathing during a rebreathing maneuver in patients with emphysema have been noted (Cournand et al. 1954), we found that the rebreathe method of measuring TLC was well tolerated. Further, as noted in the online data supplement, numerous emphysema patients were excluded from data analysis due primarily to inability to obtain a reliable single breath maneuver because of a low FEV_1 or IVC. Such constraints are not present with the rebreathe measurement.

The current study does not specifically address the use of high resolution computed tomography which has also been utilized as a “gold standard” to measure lung volume, and cannot determine to what extent emphysematous areas of the lung represent potentially recruitable gas dilution volume (Webb et al. 1988; van der Lee et al. 2006). In patients with COPD, single breath alveolar volume measures correlate with rebreathe volume measurements in non-emphysematous lung as defined by such high resolution CT (van der Lee et al. 2006).

Since only 17% of potentially eligible patients referred to the Pulmonary Diagnostic Unit in the time of enrollment were recruited and studied, it can be argued that selection bias existed in these data. However, all eligible patients were consecutively recruited as time permitted, and no major differences in demographics or physiologic status were evident between the group that was recruited and the patients that were not (see online data supplement), suggesting that the studied group is in fact a representative sample of the emphysema population referred for pulmonary function testing.

There was a statistically significant difference between mean single breath and rebreathe volumes in normal subjects. This mean difference was, however, only 200 ml, which is well within the limits of single breath underestimation of multi-breath volume reported in normal subjects with a normal $FEV_1/VC\%$ (Kendrick 1996). Further, the differences we report between single breath and rebreathe volumes were greatly and significantly different from those found in the emphysema group. Finally, the single breath measurements in normals were well matched with the plethysmographic measurements, as were the rebreathe measurements, suggesting that there was not a consistent flaw with the single breath methodology.

We conformed to current American Thoracic Society/European Respiratory Society guidelines and techniques regarding exhaled gas collection (Macintyre et al. 2005) in assessing VA_{SB} . Since VA_{SB} is measured with a fixed wash out volume, however, we cannot exclude the possibility that some of the measured exhaled gas sample could have included dead space gas, thus underestimating true VA_{SB} (Graham et al. 1985). In addition, recent evidence suggests that the collection of exhaled gas relatively early in the expiratory phase as per standard technique may result in an underestimation of VA_{SB} in patients with COPD and non-uniform distribution of ventilation (Prediletto et al. 2007). It is therefore fair to assume that our methodology may have exaggerated the differences between single breath and both rebreathe and plethysmographic volumes in the emphysema patients by a similar degree.

In summary, the current data quantify the extent to which a 10-second single breath helium dilution underrepresents physiologically relevant thoracic volume in patients with emphysema and expiratory airflow obstruction. The extent to which the noted discrepancies between single breath and rebreath lung volume measures are relevant to clinical management and outcomes in patients with emphysema remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Scatterplots of paired lung volumes for emphysema patients and normals. Filled circles are emphysema; open circles are normals. Solid lines are regression lines. Dashed lines are lines of identity. In 1A and 1C, the regression lines progressively deviate from the line of identity as lung volume increases in emphysema patients, but not in normals. In 1B and 1D, the regression lines approximate the line of identity for both emphysema patients and normals.

Fig. 2.

Bland-Altman plots for emphysema patients. Solid lines are mean differences. Dashed lines are 95% limits of agreement. Agreement between volumes varies systematically by lung volume for comparisons between TLC_{sb} and TLC_{pleth} (2A) and TLC_{sb} and TLC_{rb} (2C). Agreement does not vary by lung volume for comparisons between TLC_{rb} and TLC_{pleth} (2B) and FRC_{rb} and FRC_{pleth} (2D).

Fig. 3.

Age, gender, height, and BMI-adjusted TLC_{SB} (as a percentage of TLC_{pleth} and TLC_{RB}) and TLC_{RB} (as a percentage of TLC_{pleth}) by FEV₁% quartile for emphysema patients and normals. P values are for the interaction between FEV₁% (as a continuous measure) and respective lung volume. P values < 0.05 indicate that lung volume agreement varies by FEV₁%. Quartile 1 = lowest quartile for FEV₁%.

Table 1**Cohort Characteristics – Demographic**

Variable	Emphysema	Normal
No.	55	21
Age (years)	65 ± 7	35 ± 10
Height (cm)	167 ± 9	173 ± 9
Weight (kg)	73 ± 14	71 ± 16
BMI (kg/m ²)	26 ± 4	24 ± 4
Male	33 (60%)	12 (57%)
Race/ethnicity		
Non-Hispanic white	43 (78%)	16 (76%)
Non-Hispanic black	3 (6%)	0 (0%)
Hispanic	5 (9%)	1 (5%)
Non-Hispanic Asian	1 (2%)	3 (14%)
Unspecified	3 (5%)	1 (5%)

Data are given as mean ± SD or number (percentage).

Table 2**Cohort Characteristics – Pulmonary Function**

Variable	Emphysema	Normal
FVC		
liters	2.62 ± 0.73	4.60 ± 0.79
% predicted	71 ± 16	100 ± 11
FEV ₁		
liters	1.01 ± 0.39	3.75 ± 0.65
% predicted	35 ± 13	99 ± 13
FEV ₁ /FVC (%)	39 ± 11	81 ± 5
RV/TLC (%)	58 ± 9	28 ± 5
TLC _{pleth} (liters)	6.68 ± 1.45	6.21 ± 0.92
TLC _{RB} (liters)	6.16 ± 1.60	6.30 ± 1.04
TLC _{SB} (liters)	4.43 ± 0.94	6.08 ± 0.92
FRC _{pleth} (liters)	4.62 ± 1.19	3.07 ± 0.73
FRC _{RB} (liters)	4.05 ± 1.14	3.01 ± 0.65
GOLD Stage		
I	0	NA
II	8 (15%)	NA
III	24 (44%)	NA
IV	23 (42%)	NA

Data are given as mean ± SD.

Table 3
Mean differences and 95% limits of agreement between lung volume measurements

Lung Volumes		Emphysema		Normals		p value *
		Mean difference (95% limits of agreement)	p value ‡	Mean difference (95% limits of agreement)	p value ‡	
TLC _{pleth}	TLC _{SB}	-2.2 (-4.5 to 0.0)	<0.001	-0.1 (-0.8 to 0.6)	0.20	<0.001
TLC _{RB}	TLC _{SB}	-1.7 (-4.0 to 0.5)	<0.001	-0.2 (-0.8 to 0.4)	0.008	<0.001
TLC _{pleth}	TLC _{RB}	-0.5(-2.2 to 1.2)	<0.001	0.1 (-0.7 to 0.9)	0.26	<0.001
FRC _{pleth}	FRC _{RB}	-0.6 (-2.3 to 1.1)	<0.001	-0.1 (-0.5 to 0.5)	0.42	<0.001

* P values are from Wilcoxon rank sum (non-parametric) tests comparing mean differences between emphysema and normal
† P values are from Wilcoxon signed rank (non-parametric) tests comparing lung volumes within groups (comparing mean difference versus zero).
All data are in liters