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ORIGINAL ARTICLE

A novel approach for quality control of total lung capacity in the clinical pulmonary function laboratory: A study in a veteran population

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A novel approach for quality control of total lung capacity in the clinical pulmonary function laboratory: A study in a veteran population
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Objective: Quality control in the clinical pulmonary function laboratory has been well developed for spirometry and diffusing capacity but not for the measurement of TLC. The purpose of the present study was to test two approaches to this problem. First, we compared TLC by body plethysmography (TLC_b) with a value predicted from TLC measured by multibreath helium dilution (TLC_m). Concordance between the measured and predicted values would imply the validity of the measurements. Second, we measured the test–retest variability of TLC_b, TLC_m and TLC measured by single breath helium dilution (TLC_s) to assess the consistency of the measurements.
Methodology: We performed a prospective study of 815 veterans.
Results: The prediction of TLC_b from TLC_m improved (r^2 increased from 0.44 to 0.64) when FEV_1/FVC and the difference between TLC_m and TLC_s were added to the model. The coefficient of variation for test–retest of TLC_s, TLC_m and TLC_b were 8.9, 7.1 and 5.4%, respectively. Of all tests, 5.9% were inconsistent based on pathophysiology or measurement error and attributed mostly to TLC_m.
Conclusions: Prediction of TLC_b from TLC_m was not sufficiently accurate as to be useful for quality control. Comparison of TLC_s, TLC_m and TLC_b may be useful for determining the internal data validity.

Key words: airflow obstruction, lung volume reduction, lung volumes, multiple-breath helium dilution, quality control, single-breath helium dilution, whole body plethysmography.

INTRODUCTION

The measurement of TLC provides important information in patients suspected of restrictive lung disease because TLC is used to identify a restrictive lung defect and to assess its severity. More recently, the estimation of TLC has become important because increased residual volume appears to be an important characteristic for determining suitability for lung reduction surgery in patients with COPD.[1–3] Currently, two methods of measuring TLC are used in clinical pulmonary function laboratories: body plethysmography and helium dilution.[4,5] Although the former is considered the gold standard,[6] its acceptance as the gold standard has been questioned because it can overestimate lung volumes in the presence of airway obstruction.[7,8] Other described methods (e.g. the nitrogen balance technique or a mathematical modelling technique) do not provide accurate estimates of TLC in patients with restrictive or obstructive ventilation deficits.[9,10]

Measurement of TLC by body plethysmography (TLC_b) requires the subject to sit inside a sealed body plethysmograph.[4] TLC is calculated from changes in pressure or volume that occur when the subject is instructed to pant against an occluded airway. The measurement of TLC by helium dilution involves the

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inspiration of a defined volume of helium gas and measurement of the helium concentration in a defined expired volume after distribution in the lung. The measurement of TLC by the multiple breath helium dilution technique (TLC_m) allows complete equilibration of helium within the lungs, while the single breath technique measures the TLC (TLC_s) after a breath-hold of a gas mixture containing helium.

There are several distinctions between the helium dilution and the body plethysmography methods. Body plethysmography is quicker to perform than the multibreath helium method but may be refused by the claustrophobic patient. Helium dilution underestimates total lung capacity in the presence of airways obstruction because helium does not mix with the alveolar gas in the unventilated portion of the lung.[11] TLC_m is less likely to underestimate TLC than TLC_s because there is more opportunity for the tracer gas to equilibrate with areas of lung that are poorly ventilated secondary to airways obstruction.[12] Helium dilution can also overestimate TLC in the presence of air leaks, for example as a result of a poor seal around the mouthpiece.

Because many patients in the clinical pulmonary function laboratory are likely to present with airways obstruction and because helium dilution may result in an underestimation of TLC, it would be useful to determine the likelihood of an underestimation of total lung capacity by helium dilution.

The aim of the present study was to develop a strategy for quality control based on the internal validity of the measurements made in each patient. Two approaches were used. First, we compared TLC measured by TLC_b with a value predicted from TLC measured by TLC_m. Concordance between the measured and predicted values would imply the validity of the measurements. Second, we measured the test–retest variability of TLC_b, TLC_m and TLC measured by TLC_s to assess the consistency of the measurements. For the first approach, we initially identified factors associated with differences between TLC measured by helium dilution and body plethysmography. We then used this information to develop non-linear regression models to predict TLC_b from TLC_m. For the second approach, we measured the test–retest variability of TLC_s, TLC_m and TLC_b. We then used these data to categorize each patient as to whether or not the results were consistent with measurement error or with established identifiable methodological limitations.

METHODS

Subjects

We conducted a prospective study from July 1995 to July 1998 of all patients referred for pulmonary function testing to the Pulmonary Function Laboratory at the Veterans Affairs Medical Center in Buffalo, New York, USA. Determinations were performed on patients with and without underlying pulmonary disease if they were physically able to perform all types of test. In the patients with multiple sets of measurements, only the first was included in the current analysis. Included patients were slightly younger than non-participants (62.4 *vs* 64.0 years, $P < 0.05$ by Student's *t*-test), but were similar in weight and height.

Measurement of TLC

All measurements were made by two technicians using PK Morgan equipment (Morgan, Andover, MA, USA) according to American Thoracic Society guidelines.[13] The equilibration time for helium dilution was 4 min. For body plethysmography we used a traditional two-door body plethysmograph. The FRC was calculated from the following equation:

$$FRC = (1.359 \times (Pb - 47)/\tan\alpha \times (V_b - 28 \times BSA^{1.5})/V_b)/1000 + FRC_{off} \quad (1)$$

Where Pb is barometric pressure, $\tan\alpha$ is the tangent of the linear relation between plethysmographic pressure and mouth pressure during panting against a closed shutter (closure time 3–6 s), Vb is plethysmograph volume (800 litres), FRC_{off} is the difference in volume between FRC and the lung volume at which the shutter was closed and the patient started the panting manoeuvre. BSA is body surface area calculated from:

$$BSA = (Weight^{0.475}) \times (Height^{0.725}) \times 0.0071284$$

with weight measured in kg and height in cm.[14]

We calculated the difference between TLC measured by TLC_b and TLC_m techniques. For each subject, we averaged these two measurements to obtain an estimate of the actual TLC.

$$TLC_{avg} = (TLC_b + TLC_m)/2 \quad (2)$$

The difference between TLC_m and TLC_b was normalized by TLC_{avg}:

$$\Delta TLC_{mb} = (TLC_b - TLC_m)/TLC_{avg} \quad (3)$$

The ΔTLC_{mb} is related to airways obstruction.[15] Therefore, we used the FEV_1 as a proportion of predicted normal as a measure of the degree of airways obstruction.

We surmised that the extent of any underestimation between TLC measured by TLC_s compared with TLC_m may be a predictor of ΔTLC_{mb}. This quantity (ΔTLC_{ms}) was divided by TLC_{avg}:

$$\Delta TLC_{ms} = (TLC_m - TLC_s)/TLC_{avg} \quad (4)$$

Test–retest reliability

The coefficient of variation was 5.4% for TLC_b, 8.9% for TLC_s and 7.1% for TLC_m based on a separate analysis from two measurements on 33 patients. There were no differences between technicians in TLC measured by these methods.

Statistical analysis

We used generalized additive models with cubic splines to investigate the relation between these pre-

dictors and ΔTLC_{mb} because non-linear relations were anticipated.[16] General additive models extend linear models by modelling additive non-linear relationships between the predictors and the response variable. While linear models assume that the response is linear in each predictor, additive models assume only that the response is affected by each predictor in a smooth way. The response is modelled as a sum of smooth functions in the predictors, where the smooth functions are estimated automatically using smoothers.[16] Model selection was based on the Akaike Information Criterion.[16] We compared mean values of TLC_m, TLC_b and TLC_s using paired *t*-tests. Statistical significance was accepted at the $P < 0.05$ level. The statistical program used was S-Plus.[17]

RESULTS

During the study period a total of 2744 pulmonary function tests were performed in the pulmonary function laboratory. Our analysis focuses on a sample of 1430 sets of pulmonary function tests that included both body plethysmographic and helium dilution determinations of lung volumes measured during a single visit. Of these sets 169 were repeated tests and were eliminated from the study sample. From the remaining 1261 sets of tests, patients were excluded based on the following exclusion criteria: missing data for weight ($n = 3$), DL_{CO} ($n = 93$) and forced expiratory time less than 6 s ($n = 250$). Thus, tests for a total of 815 unique patients with complete data were analysed. Patient characteristics and pulmonary function test results are shown in Table 1. All participants were men with levels of FEV_{1pred} and FEV_1/FVC that, on average, indicated mild airway obstruction. The mean TLC_m was lower than TLC_b, but the lowest values were observed for TLC_s. The differences in mean values were statistically significant for the difference between TLC_m and TLC_s ($P < 0.001$) and for the difference between TLC_b and TLC_s ($P < 0.001$). The difference between TLC_b and TLC_m was not statistically significant ($P = 0.185$).

Table 1 Patient characteristics

	Mean	(SD)*
Age (years)	61.7	(13.5)
Height (m)	1.76	(0.07)
Weight (kg)	84.7	(16.1)
FEV_1 (L)	2.39	(0.91)
FEV_{1pred} (%)	66.3	(22.0)
FVC (L)	3.57	(0.93)
FEV_1/FVC (%)	65.5	(13.2)
TLC_b (L)*	6.72	(1.32)
TLC_m (L)*	6.68	(1.35)
TLCs (L)*	5.97	(1.28)

SD, standard deviation; TLC_b, total lung capacity measured by body plethysmography; TLC_m, total lung capacity measured by multiple breath helium dilution technique; TLC_s, total lung capacity measured by single breath helium dilution technique.

Figure 1 shows the TLC measured by body plethysmography plotted against TLC measured by helium dilution. The linear relation between TLC_b and TLC_m was not strong ($r^2 = 0.44$) and even when generalized additive models were used to account for non-linearity in the relation, the r^2 was only 0.51.

In a search for variables that could account for the difference between TLC_m and TLC_b, we found that ΔTLC_{mb} is related to FEV_{1pred}, TLC_{pred} (TLC_{avg} expressed as a percentage of predicted normal), ΔTLC_{ms}, and FRC_{off}. An additive model with all of these factors incorporated into the model simultaneously, indicated that all factors contributed to ΔTLC_{mb} (Table 2). There is a linear relation between FEV_{1pred} and ΔTLC_{mb} so there is no particular level of airways obstruction associated with ΔTLC_{mb}. Nonparametric regression models did not significantly improve the overall prediction of TLC_b from TLC_m.

Because TLC_m did not predict TLC_b accurately with the model described above, we developed a generalized additive model to predict the TLC_b from TLC_m using TLC_m with 4 d.f., FEV_1/FVC with 1 d.f. and ΔTLC_{ms} with 4 d.f. as predictor variables. The predicted values of TLC_b were compared with the actual values of TLC_b and the following relation was found.

$$TLC_b = 1.0029\ (\text{SE } 0.0262) \times \text{predicted } TLC_b - 0.0201\ (\text{SE } 0.1801) \quad (5)$$

The r^2 for this relation was 0.64. This result represents a statistically significant improvement compared with the use of TLC_m alone to predict TLC_b ($P < 0.05$).

We further speculated that discrepancies between the values of TLC_b, TLC_m and TLC_s in a patient could be used to assess errors and Table 3 shows the results of the error analysis assuming that body plethysmography will be providing the highest TLC under all circumstances and that TLC_s will be lower than TLC_m. For this analysis the coefficients of variation obtained in the test–retest experiments (5.4% for TLC_b, 8.9% for TLC_s and 7.1% for TLC_m) were used. From this table, it is apparent that 94.1% of the subjects tested have consistent data or show discrepancies that can be explained by pathophysiological mechanisms. Errors of measurement that are likely to be attributable to body plethysmography, single breath helium dilution and multibreath helium dilution were 0.7, 0.6 and 4.5%, respectively. Based on this assessment, inconsistent results were more likely to occur with TLC_m than TLC_b ($P < 0.01$).

DISCUSSION

The comparison of TLC measured by multiple breath helium dilution and body plethysmographic techniques in the present study shows that the predictive equation is not sufficiently accurate to be of clinical utility and these methods cannot be used interchangeably. Our findings also indicate that measurements of TLC by both body plethysmography and helium dilution have the potential for use in determining the internal validity of clinical measurement through error analysis.

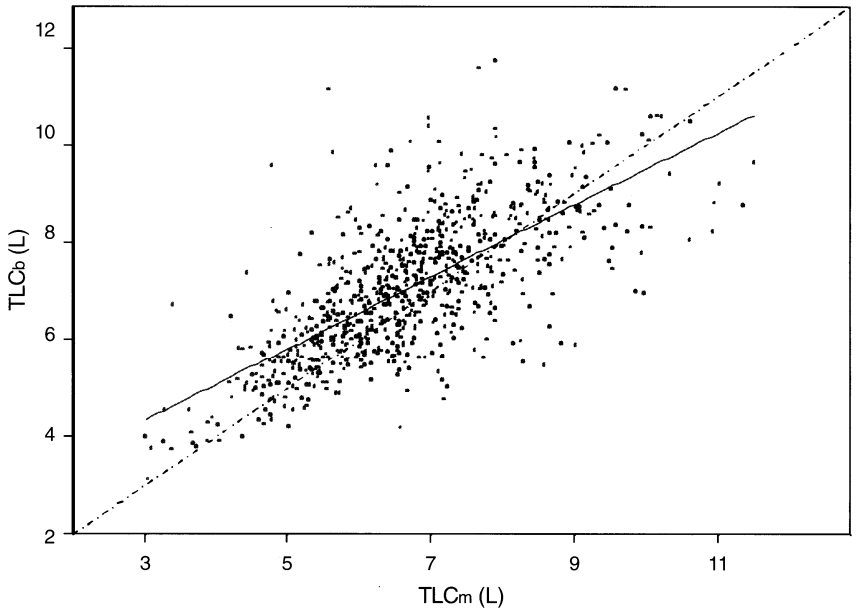

Figure 1 Scatter plot of TLC measured by whole body plethysmography (TLC_b) and TLC measured by the multiple breath helium dilution method (TLC_m). The linear regression line [TLC_b = 0.7411 (SE 0.026)* TLC_m + 2.098 (SE 0.1773)] is shown. The linear relation between TLC_b and TLC_m was not strong ($r^2 = 0.44$) and even when generalized additive models were used to account for non-linearity in the relation, the r^2 was only 0.51.

Table 2 Results of generalized additive model

Variable	Linear coefficients	Linear d.f.	Non-linear d.f.	Non-linear *P*	Linear *P*
FEV_{1pred}	−0.2357	1	0	NA	0.0015
TLC_{avg}	0.3809	1	0	NA	0.076
ΔTLC_{ms}	−0.067	1	3	< 0.001	< 0.001
FRC_{off}	0.0344	1	0	NA	0.019

d.f., degrees of freedom; linear *P*, probability of the predictor variable; non-linear *P*, probability of the non-linear component of the predictor variable; NA, not applicable. The intercept term was −0.1514.

Table 3 Quality control of measurements of TLC

Condition	Most likely but not only interpretation	Occurrence in percentage (*n*)
$TLC_b \simeq TLC_m \simeq TLC_s$	Consistent data	65.2 (531)
$TLC_b \simeq TLC_m > TLC_s$	Poorly ventilated gas space	15.3 (125)
$TLC_b \simeq TLC_m < TLC_s$	Error in TLC_s	0.3 (2)
$TLC_b \simeq TLC_s > TLC_m$	Error in TLC_m	0.6 (5)
$TLC_b \simeq TLC_s < TLC_m$	Error in TLC_m	3.1 (25)
$TLC_s \simeq TLC_m > TLC_b$	Error in TLC_b	0.7 (6)
$TLC_s \simeq TLC_m < TLC_b$	Unventilated gas space outside the lung	9.8 (80)
$TLC_b > TLC_m > TLC_s$	Unventilated gas space in and/or outside the lung	3.8 (31)
$TLC_b > TLC_s > TLC_m$	Error in TLC_s	0.1 (1)
$TLC_m > TLC_b > TLC_s$	Error in TLC_m	0.9 (7)
$TLC_m > TLC_s > TLC_b$	Error in TLC_b	0.0 (0)
$TLC_s > TLC_b > TLC_m$	Error in TLC_s,	0.3 (2)
$TLC_s > TLC_m > TLC_b$	Error in TLC_s,	0.0 (0)
Results consistent or conceivable based on pathophysiological mechanisms:		94.1 (767)
Error in TLC_m		4.5 (37)
Error in TLC_s		0.6 (5)
Error in TLC_b		0.7 (6)

TLC_b, total lung capacity measured by body plethysmography; TLC_m, total lung capacity measured by multiple breath helium dilution technique; TLC_s, total lung capacity measured by single breath helium dilution technique.

Only a moderate correlation, with considerable scatter around the line of identity, was observed between TLC_m and TLC_b, resulting in an r^2 of 0.439. We identified various factors that account for differences between the two methods of measuring TLC. These factors were FEV_{1pred}, TLC_{pred}, ΔTLC_{ms}, and FRC_{off}.

The FEV_{1pred} was anticipated to be an important predictive factor because airways obstruction may result in a reduction of lung segments that are accessible for equilibrium with helium, even with the multibreath helium dilution technique.[18] Nevertheless, it was surprising that FEV_{1pred} had a linear relation with ΔTLC_{mb} after adjustment for all other factors. Therefore, the effect of FEV_{1pred} is noticed even with minor degrees of airways obstruction. There does not appear to be a threshold level of airways obstruction where the TLC_b would be preferred over TLC_m. Reduced FEV_1 can not only result from obstructive lung disease but also from restrictive lung disease that is associated with a low FVC. In isolated restrictive lung disease the ratio of FEV_1/FVC is not reduced while obstructive lung disease is characterized by a reduction in FEV_1/FVC, but interestingly FEV_1/FVC was not as good a predictor as FEV_{1pred}. Both variables could not be used simultaneously in the prediction model because they are strongly interrelated ($r = 0.82$).

There are two reasons why TLC_{pred} is an important predictor variable. First, an elevated value suggests hyperinflation and thus provides another indicator of airways obstruction. Second, a reduced TLC_{pred} suggests restrictive lung disease. Under these circumstances, a reduced TLC_{pred} may serve to offset the effects of a reduced FEV_{1pred} that is due to restriction rather than airways obstruction.

There are several mechanisms that may result in a relation between ΔTLC_{mb} and ΔTLC_{ms}. An increased ΔTLC_{ms} could result from an increased TLC_m due to leaks during the multibreath procedure that did not occur with the single breath manoeuvre. Second, an increased ΔTLC_{ms} could result from decreased TLC_s secondary to airways obstruction resulting in occluded airspace that is accessible only during a multibreath procedure.[12] The inverse relation between ΔTLC_{mb} and ΔTLC_{ms} when ΔTLC_{ms} is positive suggests that the former mechanism dominates. A negative ΔTLC_{ms} should not exist if both measurements were conducted properly. The lack of an important relation between ΔTLC_{mb} and ΔTLC_{ms} when ΔTLC_{ms} is less than zero suggests that the TLC_s must be elevated erroneously.

Finally, the fact that FRC_{off} was a determinant of ΔTLC_{mb} was a surprise. The FRC_{off} is predominantly negative indicating that the shutter was not closed during the panting procedure exactly at end-expiration (FRC) but during the subsequent inspiration. If the shutter is closed during the inspiratory phase of the manoeuvre, the thoracic gas is rarified. As a result, thoracic gas volume, and consequently TLC_b, will be overestimated.

The mean TLC_m was lower than TLC_b, but the lowest values were observed for TLC_s. However, the difference between TLC_b and TLC_m was small. We believe that the small difference results from a preponderance of near normal pulmonary function tests. Because of the discrepancy between TLC_b and TLC_m, we developed a mathematical model to determine whether TLC_b could be predicted from TLC_m. The predictor variables were TLC_m, FEV_1/FVC and ΔTLC_{ms}. Interestingly, FEV_1/FVC was a better predictor variable than FEV_{1pred} in this model. Since the r^2 was 0.64, 36% of the variance in the difference between TLC measured by multibreath helium dilution and by body plethysmography remains unexplained by these factors. Error alone is unlikely to be the underlying reason for this unexplained variation, because similarly to others, we found that repeated measurements of lung volume by helium dilution have a coefficient of variation of less than 9%.[19] Therefore, other unknown factors must be involved that account for this variance.

We found the predictive model to be not useful because TLC measurement by body plethysmography cannot be predicted with sufficient accuracy for clinical purposes. The simultaneous measurement of TLC, however, does have some advantages for quality control when all three methods are used: body plethysmography, the multibreath helium dilution and the single breath helium dilution (Table 3).

There are potential errors that we have not addressed in the present study. For example, barometric pressure and room temperature should be measured each time the body plethysmography measurements are made. In addition, the method of adjusting plethysmographic volume for differences in the body volume of its occupants is calculated from an estimate of body surface area. Body surface area is, in turn, calculated from height and weight. A more direct approach is to calculate the plethysmograph volume, while the subject is seated within the closed plethysmograph, from the pressure swings that result when a calibrated syringe is oscillated to move a known volume of air in and out of the body plethysmograph during breath holding at functional residual capacity. However, this method is impracticable for daily routine. For the error analysis we accepted TLC measured by body plethysmography as the gold standard.[6] However, this assumption may not be true for all circumstances because TLC_b may be overestimated in airway obstruction[15,20] or in the presence of intra-abdominal gas. The equipment used in the present study applied the simplified Boyle's Law to calculate thoracic gas volume, which could have introduced error in the measurement.[21]

In conclusion, measurements of TLC by body plethysmography, single breath helium dilution and multibreath helium dilution may be useful for quality control and for determining the internal validity of clinical measurement. All methods are subject to measurement errors and the multiple breath helium dilution technique is particularly suspect in this population of veterans. Improvement in the timing of shutter closure at FRC should increase the accuracy of measurement of TLC by body plethysmography. However, in this prospective study we found that the prediction of TLC measured by body plethysmography from TLC measured by helium dilution is not sufficiently accurate to be of clinical use in the pulmonary function laboratory. Future research should focus on

the analysis of errors that occur as a result of the use of the various methods, because the exact determination of lung volume is important for clinical decision making (e.g. when patients are referred for lung reduction surgery).

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