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Total Lung Capacity with the MiniBox™: Clinical Results in Obstructed, Restrictive, and Healthy Adults

White Paper

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ABSTRACT

Among the most basic measures of respiratory function is the total lung capacity (TLC). Defined as the pulmonary gas volume at maximal lung inflation, TLC is the sum of the volume of gas that can be exhaled – the vital capacity (VC) – and the volume of gas that cannot – the residual volume (RV). Determination of VC requires only spirometry whereas determination of RV or TLC requires body plethysmography, helium gas dilution or nitrogen washout, or thoracic imaging. These techniques share the limitation of being complex and requiring a high level of patient cooperation and technical expertise to administer. We describe heretofore a new approach to determine TLC by applying an unbiased statistical model generated by data mining to flow-interruption transients and spirometry. In a heterogeneous population of 434 volunteers (265 male, 169 female; 201 healthy, 170 with mild to severe airflow obstruction, and 63 with mild to severe ventilatory restriction), we determined TLC by conventional plethysmography (TLC_{pleth}) and also by our statistical data mining approach ($TLC_{MiniBox}$). For the combined heterogeneous population, we found $TLC_{pleth} = 1.02 TLC_{MiniBox} - 0.091$ L, adjusted $r^2 = 0.824$. The coefficient of variation for repeated measurements in 26 healthy subjects on different days was 3.3% for TLC_{PLETH} versus 1.6% for $TLC_{MiniBox}$. These results establish the validity and potential utility of this new method for rapid, accurate, and repeatable determination of TLC in a heterogeneous patient population.

INTRODUCTION

The most common test of pulmonary function is spirometry, in which the volume of air flowing into and out of the respiratory system is directly measured. Spirometry can quantify volume differentials such as tidal volume (Vt), vital capacity (VC), or expiratory reserve volume (ERV), but cannot measure absolute volumes such as residual volume (RV), functional residual capacity (FRC), or total lung capacity (TLC). Although absolute thoracic gas volumes (TGV), such as RV, FRC, and TLC, are useful in the diagnosis, management and monitoring of respiratory system diseases, their measurement requires technologies that are more complex, costly and labor intensive than spirometry. Accordingly, RV, FRC, and TLC are sometimes not available in adult or pediatric office practices.

To measure absolute lung volumes, the ATS/ERS Consensus Statement identifies five methods: whole body plethysmography, multi-breath helium dilution, nitrogen wash-out, computed tomography, and chest radiography.[1] Among these, body plethysmography is used most commonly and is widely regarded as being the "gold standard".[1-8] Since its inception by Dubois in 1956[9], body plethysmography has remained elegantly simple in principle but inherently complex, capital intensive, and physically large in practice. The plethysmograph can be uncomfortable or intimidating for the patient enclosed within it and, moreover, is dependent upon a skilled technician for calibration and operation. Gas dilution or washout present different, but equally complex, challenges in test administration, including the inherently complicated logistics of maintaining and utilizing an external gas source.

Investigators have explored alternative avenues to determine TGV without success. For example, data obtained from respiratory system impedance, even when extended to a wide range of forcing frequencies, have been shown to be inadequate to infer absolute lung volumes in individual subjects.[9-16] Similarly, data obtained from forced expiratory maneuvers have been shown to be inadequate.[17] Although both methods had been reasoned to be sensitive to TGV, neither is able to determine TGV. This failure may be attributable in part to the fact that the

dynamics of gas distribution within the human lungs are complex, and especially so in obstructive lung disease. However, this failure may also be attributable in part to the fact that data interpretation often rests upon fitting respiratory impedance data to idealized mathematical models wherein there exists a wide range of TGVs that fit the data equally well. When this happens, no useful estimate of TGV can be calculated.

We utilize a completely different methodology to arrive at the TGV. We consider multiple measures of respiratory flow dynamics, all of which are restrictive to the airway opening and thus do not require body plethysmography. We then frame these multiple measures, taken together, within the context of unbiased statistical modeling. Unlike all methods described previously, many of which rest upon idealized models of respiratory system mechanics, this new approach is more akin to data mining and therefore does not require theoretical models or idealized assumptions. Herein we demonstrate that this statistical approach estimates plethysmographic TLC so closely as to comprise an accurate and repeatable stand-alone measurement of TLC without the need for body plethysmography.

METHODS

The study comprised three parts. First, in a heterogeneous population of 300 volunteers, as described below, we measured TLC in the conventional manner using body plethysmography (TLC$_{pleth}$). In those same volunteers we measured conventional spirometry and flow-interruption transients using the MiniBox[TM] (PulmOne Advanced Medical Devices, Ltd., Ra'anana, Israel). Based upon these data, we used a statistical algorithm – the LASSO[18,19] – to find the strongest set of statistical predictors of TLC$_{pleth}$. We arrived at a final statistical model with which to calculate TLC from the statistical predictors (TLC$_{MiniBox}$). Second, we validated this statistical prediction using N-fold cross-validation. Lastly, to evaluate this statistical model still further, we compared TLC$_{MiniBox}$ against TLC$_{pleth}$ in a prospective heterogeneous cohort of 134 volunteers.

Subject population. We recruited volunteers at 6 institutions (Soroka University Medical Center, Beer Sheva, Israel; Rambam University Medical Center, Haifa, Israel; Maccabi HaShalom, Tel-Aviv, Israel; Maccabi HaSharon,

Kefar-Saba, Israel; Assaf HaRofeh Hospital, Tzrifin, Israel; Tel Aviv Medical Center, Tel-Aviv, Israel) under a research protocol approved by the Ethical Review Board of each. The prospective clinical study was registered with ClinicalTrials.gov (NCT 01952431).

The population comprised three groups (Table 1): 1) healthy subjects; 2) subjects with airflow obstruction, such as chronic obstructive lung disease (COPD) or asthma and with varying severity level (mild, moderate, severe and very severe); and 3) subjects with restrictive ventilatory disorders. Patients were recruited from the Lung Function Laboratory at each institution. In each case, disease severity was defined by the criteria in ATS/ERS guidelines.[20]

Subjects were considered eligible if they: a) provided informed consent; b) were at least 18 years of age; and c) were cooperative and capable of following instructions. Healthy subjects were eligible if they: a) never smoked; b) had no known history of respiratory, cardiovascular, hepatic, renal or metabolic disease; c) had a BMI < 35 kg/m^2; d) had no persistent (lasting greater than 3 days) respiratory symptoms during the last 12 months (e.g., dyspnea, chronic cough, wheezing or phlegm); and e) had no history suggesting upper respiratory infection during the three weeks prior to testing. Non-healthy subjects were eligible if they had a documented obstructive or restrictive respiratory disorder. Subjects were excluded from the study if they: a) were pregnant at the time of the study; b) had performed any significant physical activity that has resulted in breathlessness during 1 hour prior to the study; c) had a tracheostomy; d) were unable to satisfactorily perform routine, full lung function testing including body plethysmography (e.g., due to non-compliance or claustrophobia); e) were unable or unwilling to give informed consent; or f) were unable to complete the protocol.

For each subject, all measurements were made in the same laboratory, by the same technician, and were competed within two hours. The technician also recorded the subject's gender, date of birth, height, weight, and medical history.

Body plethysmography. Different commercial body plethysmographs were used at the different study sites: a) ZAN 500 (nSpire Health, Inc) - Soroka University Medical Center, Rambam University Medical Center, Maccabi

HaSharon; b) Platinum Elite-Series (MedGraphics) – Maccabi HaShalom; c) MasterScreen Lab (Erich Jaegar, CareFusion) – Tel Aviv University Medical Center, Assaf HaRofeh Hospital. Associated transducers were calibrated in accordance with the manufacturers' user manuals.

Table 1: Basic Subject Characteristics.			
Characteristic	Entire Dataset (N = 434)	Initial Model Development (N = 300)	Prospective Validation (N = 134)
Male	265 (61.1%)	185 (61.7%)	80 (59.7%)
Female	169 (38.9%)	115 (38.3%)	54 (40.3%)
Age (years)*	45.8 ± 19.2	45.0 ± 20.1	47.8 ± 17.0
Height (cm)*	168.6 ± 9.9	168.2 ± 9.7	169.6 ± 10.4
Weight (kg)*	75.0 ± 17.3	73.6 ± 16.5	78.1 ± 18.8
Plethysmographic TLC (L)*	5.6 ± 1.4	5.6 ± 1.3	5.6 ± 1.5
Respiratory Condition: †			
Healthy	201 (46.3%)	150 (50.0%)	51 (38.1%)
Obstructed	170 (39.2%)	114 (38.0%)	56 (41.8%)
Restrictive	63 (14.5%)	36 (12.0%)	27 (20.1%)
Obstruction Severity: †			
Mild	29 (17.1%)	16 (14.0%)	13 (23.2%)
Moderate	94 (55.3%)	68 (59.7%)	26 (46.4%)
Severe	47 (27.6%)	30 (26.3%)	17 (30.4%)

* Values are means ± SD.

† Defined according to ATS standards.[20]

Device calibration and device agreement between institutions were verified using manually operated isothermal containers (3 L and 5 L) filled with copper wool, as well as by measuring a healthy control subject with a known TLC.

Body plethysmography measurements were performed in accordance with manufacturer recommendations and ATS/ERS guidelines.[1] Subjects panted at 0.5 to 1 Hz against a closed valve and then inhaled to TLC followed by slow exhalation to RV. The final thoracic gas volume (TGV) was calculated as the mean of the first 3 individual TGVs that were within 5% of each other in which the 2 highest inspiratory capacity (IC) measurements were within 10% (or 0.15 L) of each other. TLC$_{pleth}$ was calculated by adding the largest of the three ICs to the mean TGV.

MiniBox[TM]. The MiniBox[TM] (PulmOne Advanced Medical Devices, Ltd., Ra'anana, Israel) is a table-top unit that includes a spirometer and a flow-interruption device. The flow-interruption device (Figure 1A) consists of a rigid 16.3L container, a rapidly closing valve (<10 msec), and a hotwire anemometer-type flowmeter (working range +/- 5 L/s) (Figure 1B). The calibration of the MiniBox[TM] flowmeters were confirmed daily using a standard 3L syringe. No external gas source is utilized with the MiniBox[TM].

Subjects were first measured with spirometry using either the spirometer associated with the body plethysmograph or the hand-held spirometer associated with the MiniBox™. The calibration of associated flow transducers were confirmed in accordance with the manufacturers' user manuals. In addition, spirometry measurements were performed in accordance with the manufacturers' user manuals and ATS/ERS guidelines.[21] At least 3 measurements were taken with the spirometer. For SVC and forced vital capacity (FVC), the 2 highest values of the 3 measurements comprising the selected group must be within 5% (or 0.15 L) of each other. For IC, the 2 highest values of the 3 measurements comprising the selected group must be within 10% (or 0.15 L) of each other.

Subjects were subsequently measured with the MiniBox™ flow-interruption device. With cheeks manually supported and a nose clip in place, each subject sat upright in a chair and breathed through a single-use disposable bacterial filter attached to the MiniBox™ device (Figure 1A). The subject was asked to breathe normally for a short time until comfortable with the device. Then, brief flow interruptions (~70 msec) were automatically triggered in the vicinity of mid-inspiration of each tidal breath (Figure 1C). After a minimum of 25 such interruptions or a maximum of 150 seconds of tidal breathing, the subject performed a maximal inspiration twice to reach total lung capacity (TLC). The subject then exhaled slowly to residual volume (RV).

The above flow-interruption measurement was repeated up to 3 times. Volume drift was corrected assuming that FRC is stable over time. The entire measurement was deemed acceptable if the slow vital capacity (SVC) measured with the MiniBox™ device was within 10% (or 0.15 L) of the SVC measured with the spirometer. MiniBox™ flow interruption data was pre-processed and filtered based on pre-defined criteria.

Statistical model development. To construct an unbiased statistical model for TLC, we began by identifying 137 plausible metrics including transient of flows, pressures at different time points during the flow-interruption, and time derivatives of the aforementioned transient flows and pressure predictors, as well as spirometrical transients and indices, driven by a proprietary mathematical model of the lungs. This model was then tested in 300 qualified volunteers.

From these 137 metrics, we then used a statistical algorithm – the LASSO[18,22] – to find the smallest possible set of predictors that were statistically significant. The LASSO is an extension of multiple linear regression and finds a combination of parameters while forcing all but a few coefficients to be precisely zero, thereby, providing a minimal statistical model that is more readily interpretable. Here, the LASSO was accomplished using a tunable parameter that constrains the coefficients with cross-validation using random sampling with replacement (bootstrapping)[23-25] repeated 300 times for each value from a range of possible values. Each sampling was constrained according to the same ratio of male/female and healthy/non-healthy as the entire group of subjects.

Statistical model for TLC$_{MiniBox}$. Using the LASSO applied to the dataset of 300 subjects, we were able to arrive at a final statistical model to calculate TLC$_{MiniBox}$ based on flow and pressure transients resulting from the interruptions of the MiniBox**™** flow-interruption device, and spirometry.

N-fold cross-validation. To validate the appropriateness of the selected metrics, N-fold cross-validation was used on the dataset of 300 subjects. The dataset was randomly divided using 5-fold and 10-fold, each for 50 times, and the samples for each fold were selected randomly for each time. All parameters were found to contribute significantly to the model (p<0.001).

Prospective validation. Beyond the internal N-fold cross-validation, we performed an independent prospective study to further validate the TLC$_{MiniBox}$ equation resulting from the MiniBox**™** measurements. In a prospective heterogeneous cohort of 134 additional volunteers not previously studied (Table 1), we repeated the protocol of MiniBox**™** and body plethysmography measurements. We then used the new TLC$_{MiniBox}$ equation derived from the initial cohort of 300 to calculate TLC$_{MiniBox}$ and compare it to TLC$_{pleth}$.
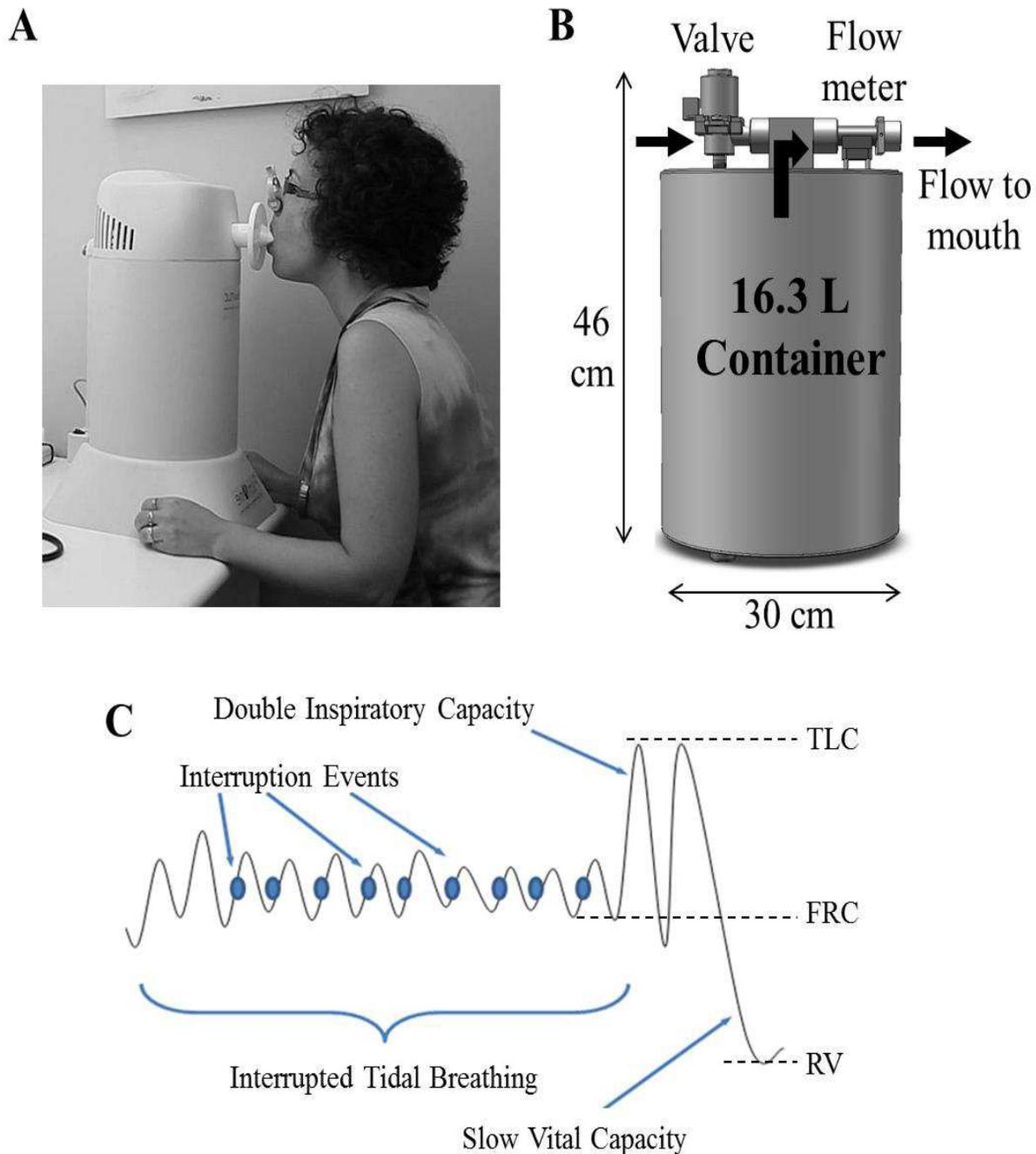
Figure 1: Overview of the MiniBox™ flow-interruption device and associated measurement procedure. a) Photograph of the MiniBox™ flow-interruption device during operation. The device sits on a table-top and the subject breathes tidally through a viral bacterial filter. **b)** Schematic illustration of the components of the MiniBox™ flow-interruption device, depicting the relative positions of the cylindrical container, valve, and flowmeter. Arrows indicate the direction of flow during inspiration. **c)** Schematic illustration of the standard breathing pattern during a MiniBox™ flow-interruption measurement. Increasing lung volume is shown on the vertical axis and time increases to the right. During tidal breathing, brief interruptions are triggered in the vicinity of mid-inspiration (dots). After a minimum of 25 such interruptions or a maximum of 150 seconds, the subject then inhales maximally to TLC twice (double inspiratory capacity) and then exhales slowly to RV (slow expiratory vital capacity).

RESULTS

Subject characteristics. 564 subjects were enrolled, of whom 4 were unable to complete the protocol and 126 were disqualified by quality assurance criteria. There were no adverse events. The final qualified dataset comprised 300 subjects in the first cohort and 134 subjects in the prospective cohort (Table 1). Both cohorts included healthy individuals and patients with a range of diseases and a range of disease severities.

TLC$_{MiniBox}$ versus TLC$_{pleth}$. Across the entire mixed population of 300 qualified subjects, TLC$_{MiniBox}$ tracked TLC$_{pleth}$ closely (Figure 2A; TLC$_{pleth}$ = 1.02TLC$_{MiniBox}$ – 0.091 L, adjusted r^2=0.824).   In the subset of 150 healthy individuals, the variability was minimal (Figure 2B; TLC$_{pleth}$ = 0.991TLC$_{MiniBox}$ + 0.0414 L, adjusted r^2=0.852) while in the subset of 114 obstructed subjects (Figure 2C; TLC$_{pleth}$ = 1.02TLC$_{MiniBox}$ – 0.004 L, adjusted r^2=0.739) and in the subset of 36 restrictive subjects (Figure 2D; TLC$_{pleth}$ = 0.844TLC$_{MiniBox}$–0.474 L, adjusted r^2=0.653), the variability was somewhat greater.   Nonetheless, in each of these subpopulations, TLC$_{MiniBox}$ closely tracked TLC$_{pleth}$.

We performed Bland-Altman[26] analyses to examine differences between results from both methods in relation to lung size. In the population as a whole (Figure 2E), and in each of the subpopulations (healthy - Figures 2F; obstructed - Figure 2G, and restrictive - Figure 2H), the coefficients of variations were 9.91%, 7.93%, 11.30%, and 13.70% respectively; the mean biases were small (0.01 L, -0.01 L, 0.11 L, and 0.20 L, respectively). There was no systematic trend of variability or bias with lung size.

Day-to-day repeatability of TLC$_{MiniBox}$. From the initial 300 subject pool, we selected 26 healthy subjects at random to assess day-to-day repeatability with a minimum of 12 days between the measurements. Day-to-day repeatability was expressed as a coefficient of variation (CV; Figure S2). For TLC$_{pleth}$, the CV was 3.3% whereas the CV for TLC$_{MiniBox}$ was 1.6%.

Further validation in the prospective cohort. To further validate TLC$_{MiniBox}$, we used the statistical model equation derived from the original cohort of 300 patients to calculate TLC$_{MiniBox}$ for each member of a prospective cohort of 134 (Figure 3). In this prospective cohort, TLC$_{MiniBox}$ closely tracked TLC$_{pleth}$ and followed similar regression lines and confidence intervals, although slopes and the adjusted r^2 were slightly lower.

DISCUSSION

Body plethysmography is a complex, expensive and cumbersome procedure to perform in clinical practice. In addition, although gas dilution devices do not require a body chamber, they are dependent on external gas sources for their operation. Our objective was to establish a clinically useful tool to measure TLC that does not require a body chamber nor external gas sources, and can be operated as easily as a spirometer.

To accomplish this, we reviewed the scientific literature in which it has been known that flow dynamics measured at the airway opening, as in respiratory impedance or flow interruption, are sensitive to lung volume but when these measurements are taken individually, none is sensitive enough to determine the TLC.[27] We overcame these previous limitations by applying advanced statistical data mining approaches using modern day computing power, and were able to extract key pieces of PFT data that when combined in a unique mathematical fashion can determine TLC with clinical accuracy. The end result is an approach to determine TLC that its clinical outcome may be far more practical. Below, we further describe the data mining approach to calculate TLC and the potential clinical utility of the MiniBox^{TM}.

Data mining in the context of respiratory mechanics. Using data mining across a heterogeneous population of patients, we identified certain features – in this case features of flow dynamics – that are associated on purely statistical grounds with TLC$_{pleth}$. Rather than focus on respiratory mechanics and physiology, we applied lessons of data mining and epidemiology to understand which components of pulmonary function testing contribute most to the outcomes. Hence we were able to compose a revolutionary and highly accurate technique to measure lung volumes.
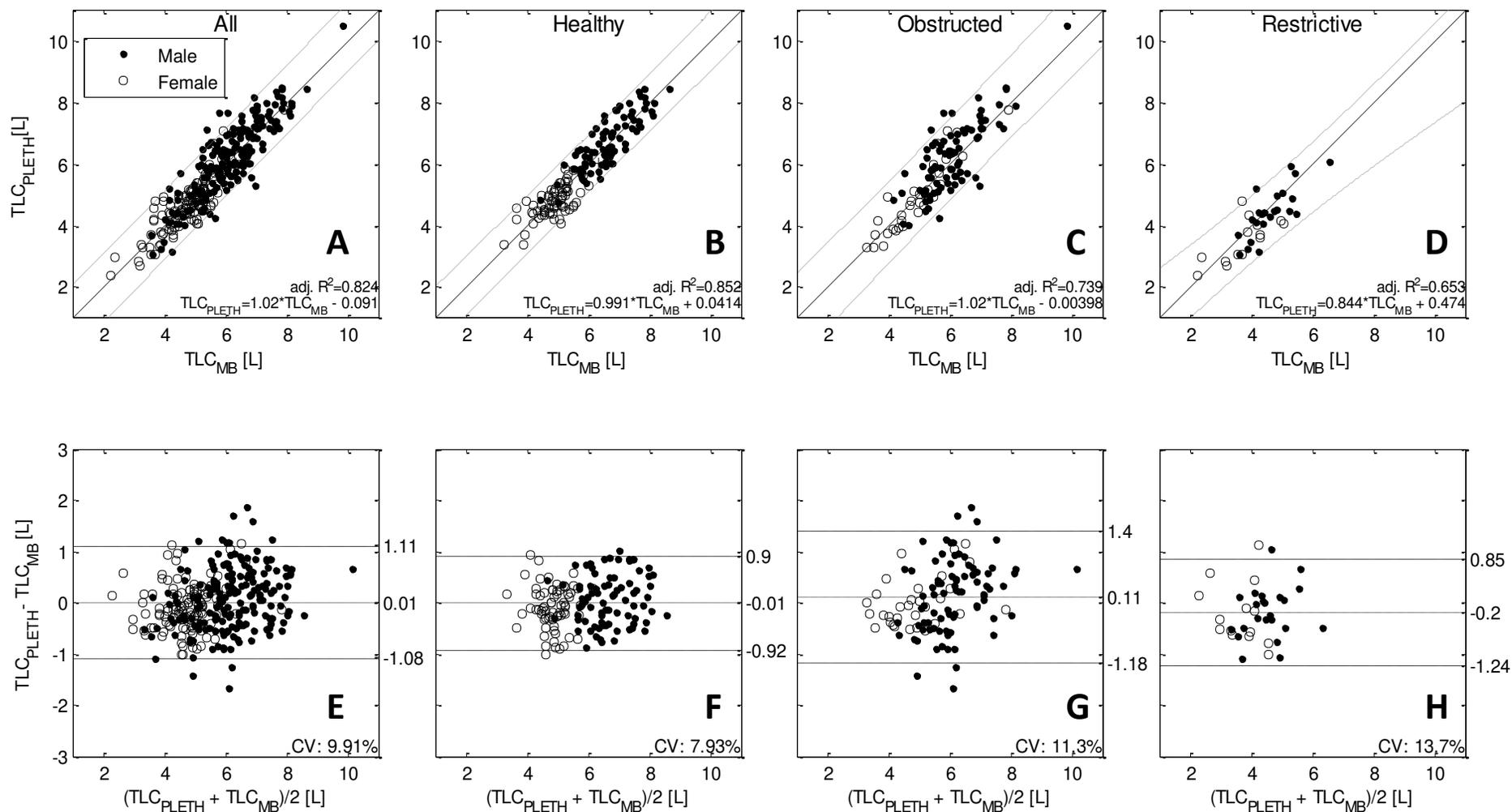
Figure 2: Initial validation of MiniBox's TLC$_{MiniBox}$ or TLC$_{MB}$ (300 subjects). (Top: A, B, C, D) Scatter plots of plethysmographic TLC (TLC$_{PLETH}$) vs. MiniBox™ TLC (TLC$_{MB}$) for all subjects, healthy subjects only, obstructed subjects only, and restrictive subjects only. Males are represented by closed circles and females are represented by open circles. For subjects that were measured more than once on the device, the TLC is presented as the average value of all measurements. The dashed lines represent the unity line and the dotted lines represent the confidence intervals. The linear regression equation and the adjusted R^2 are displayed within each graph. **(Bottom: E, F, G, H)** Associated Bland-Altman plots comparing MiniBox™ TLC to plethysmographic TLC for all subjects, healthy subjects only, obstructed subjects only, and restrictive subjects only. The solid lines represent the mean bias while the dashed lines represent the upper and lower limits (±1.96*SD). The mean coefficient of variation (CV) is displayed within each graph.
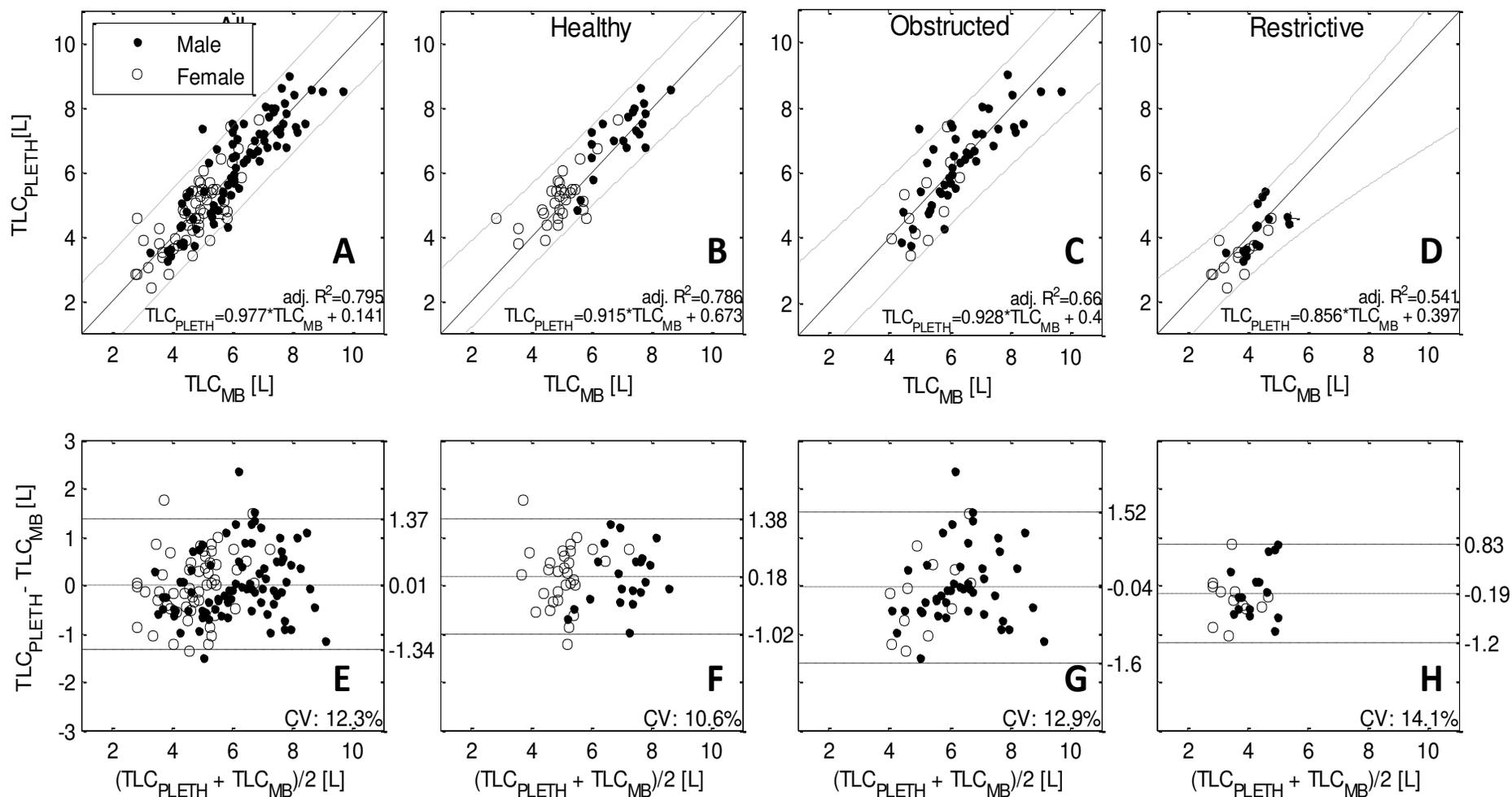
Figure 3: Independent, prospective validation of MiniBox TLC (134 subjects). **(Top: A, B, C, D)** Scatter plots of plethysmographic TLC (TLC_{PLETH}) vs. MiniBox™ TLC (TLC_{MB}) for all subjects, healthy subjects only, obstructed subjects only, and restrictive subjects only. Males are represented by closed circles and females are represented by open circles. For subjects that were measured more than once on the device, the TLC is presented as the average value of all measurements. The dashed lines represent the unity line and the dotted lines represent the confidence intervals. The linear regression equation and the adjusted R^2 are displayed within each graph. **(Bottom: E, F, G, H)** Associated Bland-Altman plots comparing MiniBox™ TLC to plethysmographic TLC for all subjects, healthy subjects only, obstructed subjects only, and restrictive subjects only. The solid lines represent the mean bias while the dashed lines represent the upper and lower limits (±1.96*SD). The mean coefficient of variation (CV) is displayed within each graph.
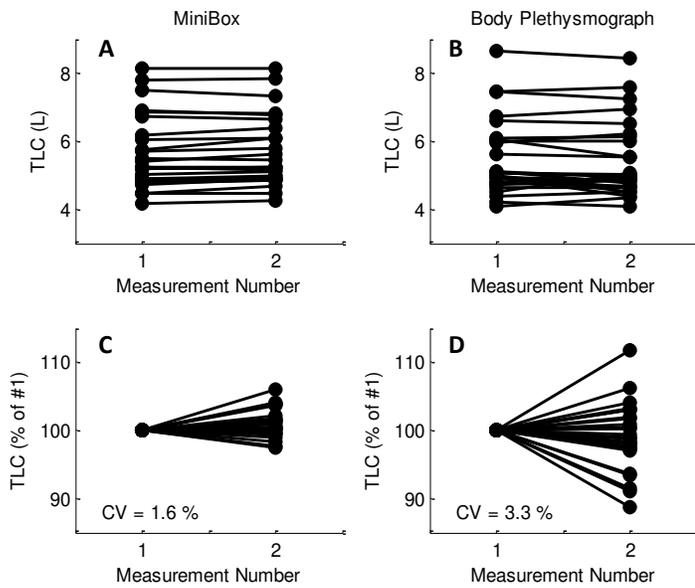
Figure 4: Repeatability of MiniBox[TM] and Plethysmographic TLCs measured on two different days. (Top: A, B) TLC measured on day 1 and day 2 with the MiniBox[TM] and the body plethysmograph. (Top: C, D) TLC normalized to the day 1 value. In 26 healthy subjects, the MiniBox[TM] day-to-day repeatability was 1.6% compared to 3.3% for body plethysmograph.

Summary of clinical results. Our results show that $TLC_{MiniBox}$ is remarkably accurate compared to TLC_{pleth} across the entire population studied and across specific patient subgroups. Among our prospective cohort of 134 subjects, who were healthy or had varying severities of obstructive and restrictive diseases, $TLC_{MiniBox}$ correlated well with TLC_{pleth} (adjusted r^2 = 0.795) with a slope close to unity (slope = 0.977) (Figure 3). Furthermore, in a subset of healthy subjects, $TLC_{MiniBox}$ was appreciably more repeatable from day-to-day than was TLC_{pleth} (Figure 4), suggesting that $TLC_{MiniBox}$ may likely be useful in longitudinal clinical management.

Comparison to helium dilution and CT imaging. It is also important to understand how the MiniBox[TM] compares to other alternative technologies to measure absolute lung volumes, namely helium dilution and computed tomography (CT). In a cohort of healthy, obstructive, and restrictive subjects, O'Donnell et al. performed Bland-Altman analyses to compare TLC measured using both helium dilution (TLC_{He}) and CT imaging (TLC_{CT}) to TLC measured using plethysmography (TLC_{pleth}).[6] For TLC_{He} and TLC_{CT}, the analysis showed coefficients of variation of 18.9% and 15.6%, respectively, together with systematic biases and trends for increasing error in subjects with larger TLCs (Figure 5B and 5C). Although we studied a different cohort, and results may therefore not be strictly comparable, Bland-Altman analysis of $TLC_{MiniBox}$ showed a coefficient of variation of 12.1% in our prospective cohort (N = 134 subjects), no systematic bias, and no trend of
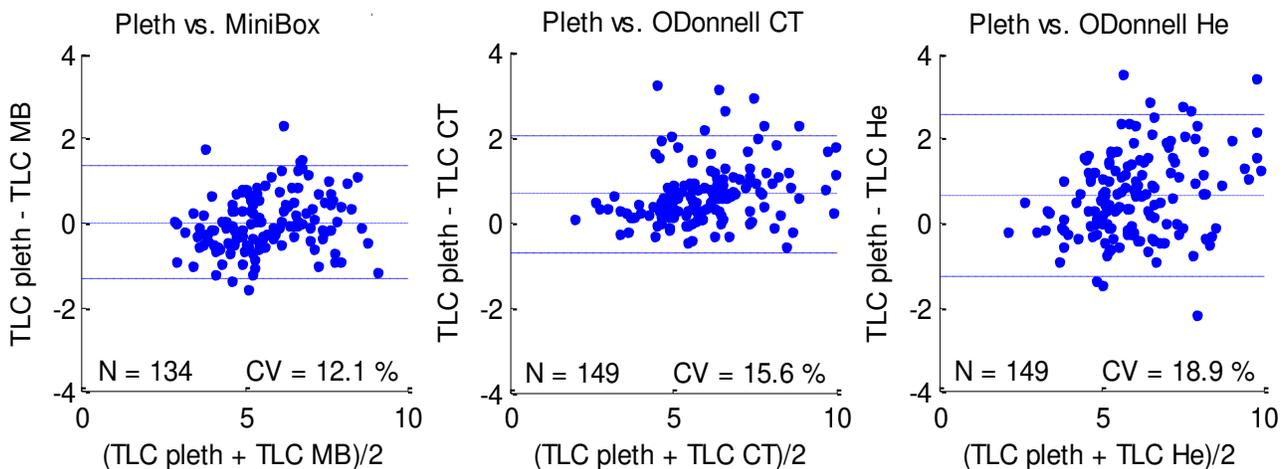

Figure 5: Bland-Altman Plots for MiniBox[TM] TLC, CT TLC, and Helium TLC compared to Plethysmographic TLC. In comparison to plethysmographic TLC, the absolute errors in MiniBox[TM] TLC are smaller than the errors in CT TLC and Helium TLC.

increasing error with increasing TLC (Figure 5A). While each of these technologies is based on a different mechanism-of-action, and thus, is not expected to mimic plethysmographic TLC faithfully in all subjects, TLC$_{MiniBox}$ values had the smallest deviations from those of TLC$_{pleth}$.

Potential clinical utility. While the NHLBI, ATS, and ERS have encouraged innovation in technologies to measure absolute lung volumes[28], these organizations recommend rigorous testing of new technologies to ensure they do not differ substantially from standard techniques, as well as to show that the new technologies offer advantages specifically in terms of improved accuracy, ease of use, and rapidity of testing. As evidenced by our data, the MiniBox^{TM} performs quite similarly to body plethysmography in all measured sub-populations. Also, the MiniBox^{TM} outperforms helium dilution and CT imaging approaches and surpasses body plethysmography on day-to-day repeatability, which may be particularly useful for longitudinal chronic pulmonary disease management. Lastly, as it requires no external gas source and does not require a subject to sit within an airtight chamber, the MiniBox^{TM} may provide the clinician with a faster and easier-to-use tool to determine TLC. This may be particularly useful for lung volume measurements in routine office practice. The current standard for monitoring obstructed patients is with spirometry alone, whereasthe MiniBox^{TM} will permit the clinician to trend lung volumes and identify hyperinflation earlier on in the disease process.

Conclusions. This study establishes the validity of TLC$_{MiniBox}$ measured with the MiniBox^{TM} for rapid, accurate, and repeatable determination of TLC in a heterogeneous population of healthy adults and those with respiratory system diseases.

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