

Validation of a Novel Compact System for the Measurement of Lung Volumes



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BACKGROUND: Current techniques for measuring absolute lung volumes rely on bulky and expensive equipment and are complicated to use for the operator and the patient. A novel method for measurement of absolute lung volumes, the MiniBox method, is presented.

RESEARCH QUESTION: Across a population of patients and healthy participants, do values for total lung capacity (TLC) determined by the novel compact device (MiniBox, PulmOne Advanced Medical Devices, Ltd.) compare favorably with measurements determined by traditional whole body plethysmography?

STUDY DESIGN AND METHODS: A total of 266 participants (130 men) and respiratory patients were recruited from five global centers (three in Europe and two in the United States). The study population comprised individuals with obstructive ($n = 197$) and restrictive ($n = 33$) disorders as well as healthy participants ($n = 36$). TLC measured by conventional plethysmography (TLC_{Pleth}) was compared with TLC measured by the MiniBox (TLC_{MB}).

RESULTS: TLC values ranged between 2.7 and 10.9 L. The normalized root mean square difference (NSD) between TLC_{Pleth} and TLC_{MB} was 7.0% in healthy participants. In obstructed patients, the NSD was 7.9% in mild obstruction and 9.1% in severe obstruction. In restricted patients, the NSD was 7.8% in mild restriction and 13.9% in moderate and severe restriction. No significant differences were found between TLC values obtained by the two measurement techniques. Also no significant differences were found in results obtained among the five centers.

INTERPRETATION: TLC as measured by the novel MiniBox system is not significantly different from TLC measured by conventional whole body plethysmography, thus validating the MiniBox method as a reliable method to measure absolute lung volumes.

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KEY WORDS: novel measurement; physiology; plethysmograph; pulmonary function test; total lung capacity

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ABBREVIATIONS: ATS = American Thoracic Society; ERS = European Respiratory Society; FRC = functional residual capacity; NSD = normalized root mean square difference; RV = residual volume; TLC = total lung capacity; TLC_{MB} = total lung capacity measured by the MiniBox; TLC_{Pleth} = total lung capacity measured by plethysmography

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Take-home Points

Study Question: Across a population of patients and healthy participants, do values for total lung capacity (TLC) determined during tidal breathing by a novel compact device (MiniBox) compare favorably with measurements determined by traditional whole body plethysmography?

Results: The novel MiniBox system yielded accurate and reproducible determination of TLC as compared with the current gold standard plethysmography technique (normalized standard difference, 8.5%; mean discrepancy, -0.05 L) without the need for ionizing radiation or inhalation of inert gases.

Interpretation: The MiniBox system should be considered a clinically reliable technique to obtain measurement of lung volumes that are equivalent to plethysmography in both healthy participants as well as those with lung disease.

Measurement of absolute lung volumes, specifically residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC), are useful in the diagnosis and management of respiratory disorders as a supplement to simple spirometry. However, determination of these volumes requires more complex and expensive technologies than those used for spirometry. Consequently, many clinics in private and hospital settings rely on results of spirometry alone when assessing lung function, which is not in accord with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.¹

Five methods currently are available for measuring absolute lung volume: whole body plethysmography, multibreath helium dilution, nitrogen washout, CT scanning, and chest radiography. Each technique has advantages and disadvantages to the clinician and the patient. CT scanning and chest radiography are not used in pulmonary function laboratories and incur radiation exposure, whereas helium dilution and nitrogen washout may underestimate lung volumes because gas may not distribute fully to poorly ventilated areas. Body plethysmography may overestimate lung volume relative to other measurements,² primarily in the setting of airflow obstruction and increased compliance of the extrathoracic airway.³ Several comparative studies have demonstrated

differences between the gas-based techniques (helium dilution and nitrogen washout) and plethysmography with a normalized root mean square difference (NSD) ranging between 8.8% and 23.7% (Fig 1).²⁻¹¹

Whole body plethysmography is simple in principle but inherently complex in practice because patients must sit inside a sealed booth and perform a complex respiratory maneuver against a closed shutter (ie, an occluded airway). Although gas dilution and gas washout techniques are well-established alternatives to plethysmography, they require more time to demonstrate repeatability between maneuvers, especially in patients with obstructive airway diseases. Moreover, these gas-based techniques correlate well with plethysmography only in healthy participants, but underestimate lung volumes in patients with airflow obstruction.^{2,3,6,7,12}

Until recently, the search for practical alternatives to plethysmography has remained unsuccessful. Imaging techniques are not practical everyday tools because of availability, cost, and radiation exposure.^{2,8-10}

Respiratory system impedance, even when extended to a wide range of forcing frequencies, cannot yield estimates for absolute lung volumes.¹³⁻¹⁵ Similarly, forced expiratory maneuver techniques are inadequate.⁵ These failures may reflect the complex dynamics of gas distribution within the lung, particularly in participants with obstructive diseases.

The MiniBox (PulmOne Advanced Medical Devices, Ltd.) is a new Food and Drug Administration-approved device that is not yet included in ATS/ERS guidelines.¹⁶ The MiniBox is a table-top unit that includes a flow-interruption device and a rigid container (Fig 2). Like plethysmography, it measures lung volumes in a manner that does not require radiation, forced maneuvers, or inhalation of inert gases. The MiniBox derives TLC during tidal breathing by analysis of gas pressures and air flows immediately preceding and following airway occlusions based on a combination of first principles and inductive statistics. The present study was designed to evaluate the measurement bias and equivalency between TLC determined by the novel compact device (MiniBox) and measurements determined by traditional whole body plethysmography across a population of patients and healthy participants.

Methods

To validate the MiniBox technique we recruited an international group of investigators based in Europe (Enschede, The

Netherlands; Barcelona, Spain) and North America (New York, New York, and Burlington, Vermont) and compared TLC measured by the MiniBox (TLC_{MB}) with TLC measured by plethysmography (TLC_{Pleth}). A nonsponsored center (Verona, Italy)

also participated in the study and adhered to the same protocol as the other four centers.

Participants

The study population comprised three groups of adult participants (age, ≥ 18 years): (1) healthy participants, (2) patients with airflow obstruction (FEV_1 to FVC, < 0.70), and (3) patients with restrictive ventilatory disorders. Disease severity varied and was defined based on ATS/ERS guidelines.¹ Participants were recruited either from referrals to the lung function laboratory, from referrals to the pulmonary outpatient clinic, or both. Healthy participants were recruited either by word of mouth (Vermont site) or from among healthy individuals who were referred for pulmonary function testing (other sites). Each site used different plethysmography devices, allowing analysis for site and device dependence. Each site's research ethics committee approved the study.

All participants provided informed consent and were capable of following instructions. Pregnant women were excluded. Healthy

participants were recruited based on: (1) no smoking history (< 5 pack-years), (2) BMI < 30 kg/m², (3) absence of wheeze, (4) absence of respiratory symptoms (breathlessness, cough, or sputum), (5) no history of asthma or response to either bronchodilator or methacholine, and (6) absence of recent respiratory tract infection (within 6 months).

Study Protocol

Participants first performed spirometry using either the plethysmograph or the MiniBox spirometer. Each participant's year of birth was used to assign which device to use first; plethysmography was used first in individuals born in an even year, and the MiniBox was used first in individuals born in an odd year. Testing was performed by pulmonary function technicians, research coordinators (all with advanced degrees including nursing, registered pulmonary function technologist certification, and baccalaureate degrees), or both who specifically were trained to perform both spirometry and plethysmography testing procedures. All measurements conformed with ATS/ERS guidelines.^{17,18} For slow

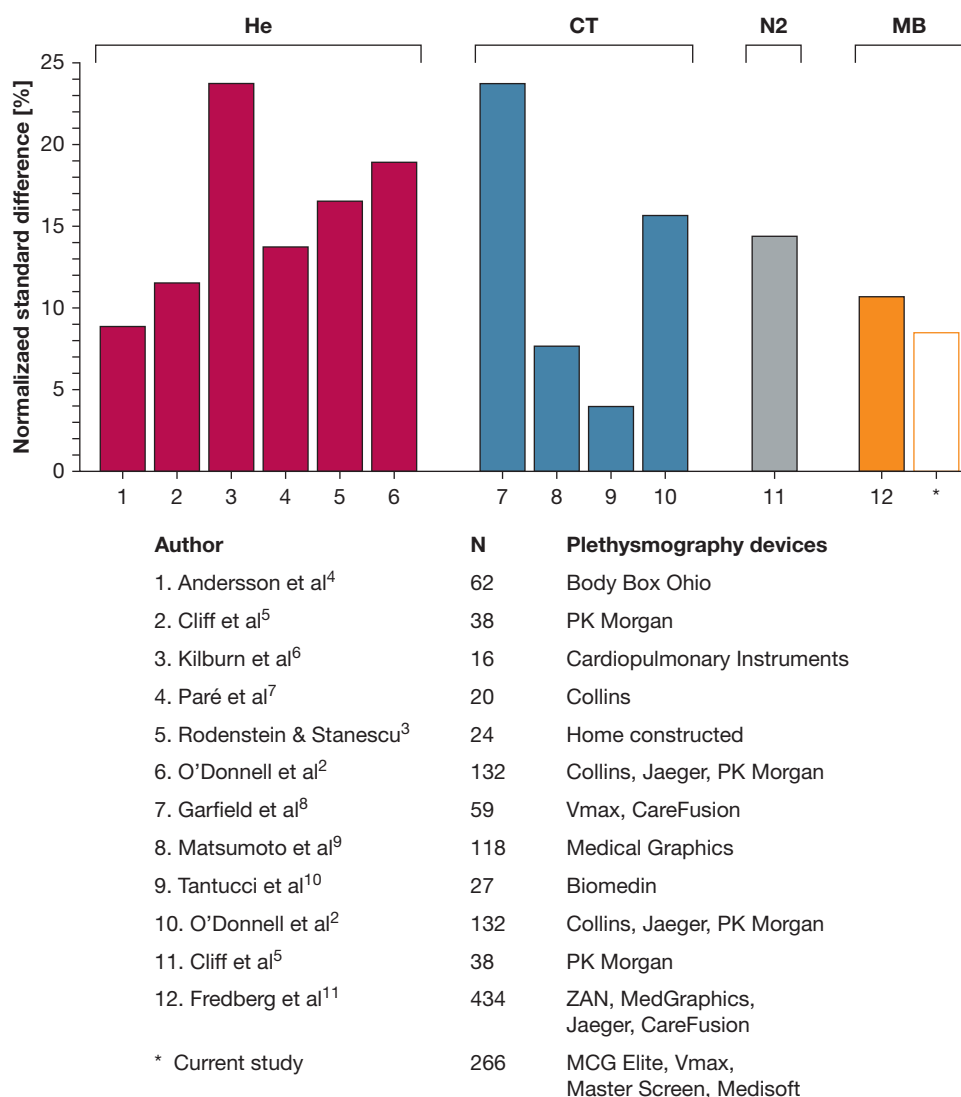


Figure 1 – Bar graph showing the NSD for TLC data when body plethysmography was compared with those obtained using He, N₂, CT scanning, and the MB systems. Also shown are the number of participants (N) and the plethysmography devices in each study. Of note, the NSDs were calculated for these published studies using the identical definition that was applied in the present study. He = helium dilution; MB = MiniBox; N₂ = nitrogen washout; NSD = normalized root mean square difference; TLC = total lung capacity.

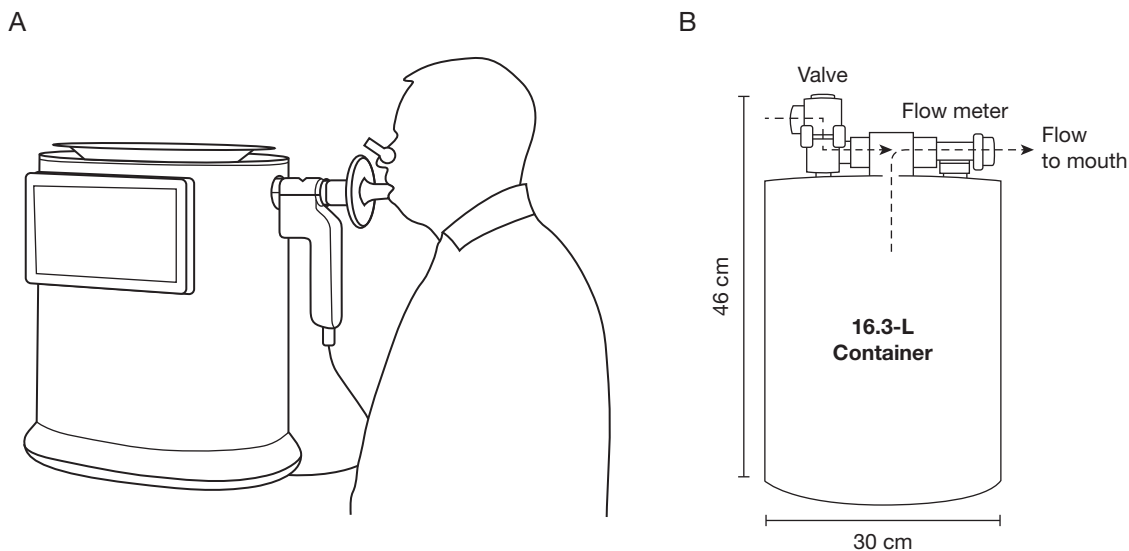


Figure 2 – Illustrations of MiniBox device. A, Patient breathing through mouthpiece of the MiniBox, with the spirometer and the tablet computer (both detachable) attached to the device. B, Schematic of the device setup and airflow during the inhalation phase. When the valve is closed, air flows from the rigid container to the lungs, causing a pressure drop in the container.

vital capacity and FVC, additional maneuvers were performed until the two highest values were within 0.15 L and 5% of each other.

Body Plethysmography

Body plethysmography devices varied by center (Barcelona, Medisoft, BodyBox, Sorinnes, Belgium; Vermont and Verona, MGC Diagnostics Elite, body plethysmograph, Saint Paul, MN; New York, Vyaire Vmax Encore, Yorba Linda, CA and Enschede Vyaire Master Screen (MasterScreen PFT System, Yorba Linda, CA). Measurements conformed with ATS/ERS guidelines.¹⁸ Participants panted at FRC against a closed valve to measure thoracic gas volume, and then inhaled to full inspiration followed by slow exhalation to full expiration to calculate TLC and RV, respectively. Multiple thoracic gas volume measurements were obtained until repeatability met ATS/ERS guidelines.¹⁸

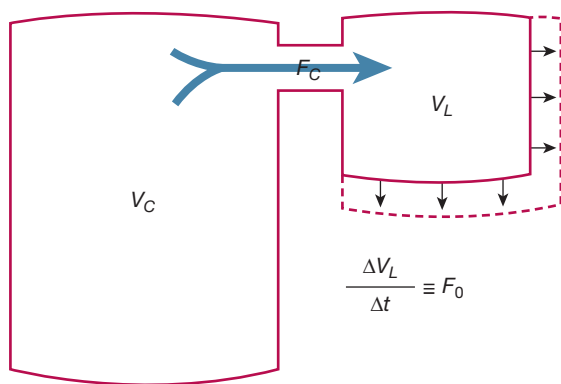


Figure 3 – Diagram showing the physical basis of the MiniBox method. A rigid container of volume V_C is connected to a container of volume V_L which expands at the rate F_0 . Here V_L mimics the lungs and V_C mimics the volume of the MiniBox device. The rarefaction of gas in the expanding system induces a flow of gas F_C from the rigid container to the expanding container.

MiniBox Device

The MiniBox device comprises a detachable spirometer, a rigid container and tubing (total, 16.3 L), and a rapidly closing valve (< 15 msec) (Fig 2). The spirometer consists of two differential manometers with low and high dynamic ranges of ± 1.25 and 7 L/s, respectively. MiniBox flowmeter calibration was performed daily using a 3-L syringe.¹⁷

With a nose clip in place, each participant sat upright and breathed through a disposable bacterial and viral filter. TLC_{MB} was measured up to three times, with a final result provided without operator intervention based on automatic postprocessing of the flow data. The measurement was deemed acceptable if the slow vital capacity measured during the TLC_{MB} maneuver was within 0.15 L and 10% of the slow vital capacity measured by spirometry.

Description of the Novel Method

Physical Basis of MiniBox Method: As in traditional plethysmography, the MiniBox method is based on noninvasive measurements of gas pressures and flows.^{11,19} Although the final determination of TLC by the MiniBox method depends on empirical adjustments that remain proprietary, the selection of measured parameters is guided by a physical model, as described below and in e-Appendix 1. The physical model derived here (Equation S17, E-Appendix 1) provides insights regarding the relationship of lung volumes to the flow interruption signal.

Figure 3 shows an idealized representation of the lung and MiniBox system during inhalation of air through the device with the valve closed (Fig 2A). The idealized system consists of a container with fixed volume, V_C , connected to a smaller container with volume V_L that expands at a rate of F_0 . The fixed-volume container represents the MiniBox rigid container, the expanding volume represents the expanding lungs, and the flow in the tube connecting the two containers (F_C) caused by evacuation of air from the rigid container represents flow at the mouth (Fig 2B). In a closed system, the ratio of the expanding and rigid volumes (V_L to V_C) is in proportion to the ratio of the expansion and evacuation rates (F_0 to F_C) and to some measure of total system impedance. Further, the lungs are characterized by isothermal conditions (ie, Boyle's law), whereas

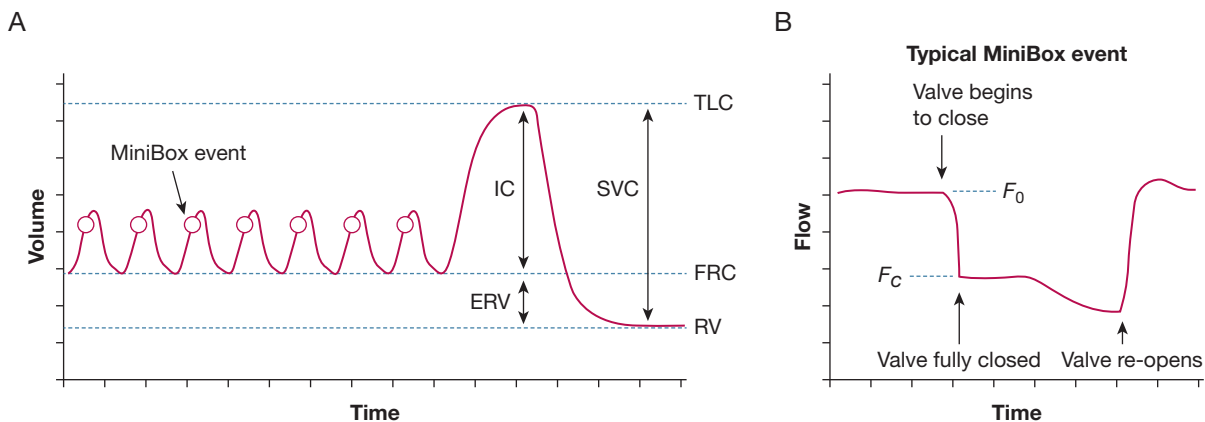


Figure 4 – Graphs showing breathing maneuvers and events of the MiniBox. A, Minibox events (circles) are triggered toward the end of the inhalation phase of normal breathing. B, Airflow during a typical MiniBox event. The flow levels F_0 and F_C are calculated by averaging (over intervals of approximately 20 ms) the flow just before the valve begins to close and right after the valve fully closes. ERV = expiratory reserve volume; FRC = functional residual capacity; IC = inspiratory capacity; RV = residual volume; SVC = slow vital capacity; TLC = total lung capacity; VC = vital capacity.

variations in the container are approximately adiabatic (ie, internal energy is conserved). As shown in e-Appendix 1, combining these constraints yields the following model for predicting V_L :

$$V_L = V_C \phi \left(\frac{F_0}{F_C}, \alpha, R \right), \quad (1)$$

where ϕ is a function of the unitless parameters F_0 to F_C , α , and R . The parameter α is a measure of the ratio of specific heats of the lung and container, which describes differences between the thermodynamic conditions in the lungs and container. The parameter R is a measure of the lung-container system impedance. The physical parameters α and R , as well as the specific functional form of ϕ , are determined empirically using plethysmography measurements of lung volume as reference.^{11,19} More details on the physical assumptions of the method and on the derivation of Equation 1 are provided in e-Appendix 1.

MiniBox Measurement of TLC: TLC_{MB} is calculated from physiologic parameters together with a series of short flow interruption events (termed *MiniBox events*) activated during the inhalation phase of normal breathing. e-Appendix 1 provides a detailed description of how the parameters in Equation 1 are determined during these MiniBox valve closure events. Briefly, the MiniBox maneuver is shown in Figure 4A. Flow is measured continuously at the mouth, thus tracking relative changes in lung volume. The participant first breathes normally (≥ 3 breathing cycles) to train the device to identify breathing cycles and to acclimatize themselves to the device. After these initial breathing cycles, the device automatically triggers MiniBox events after mid inspiration of each breathing cycle. After a minimum of six such events, the participant performs maximum inspiration to TLC, followed by exhalation to RV. The MiniBox events consist of rapid closure of the valve, after which air is evacuated from the rigid container by the lungs, followed by rapid reopening of the valve (after approximately 70 ms) and return to uninterrupted breathing (Fig 4B). For each event, TLC is calculated as the instantaneous lung volume during the event plus the volume inhaled to TLC; the average of these data is reported as the final TLC_{MB} .

Relationship of MiniBox Method to Plethysmography: Both traditional plethysmographic methods and the MiniBox method rely on measurements of pressures and flows. For that reason and others,

the tendency of plethysmography to overestimate TLC in patients with chronic obstructive lung disease⁵ is expected also to exist with the MiniBox. Similarly, TLC_{MB} is susceptible to errors resulting from nasal and oral air leaks.²⁰

Statistical Analysis

The correlation between the two methods of measuring TLC was calculated using a two-tailed t test, with a significance level of 5% ($P < .05$). The difference between groups of patients was assessed by calculating the difference between TLC_{MB} and TLC_{Pleth} for each patient and using single-factor analysis of variance for comparing the groups of patients (F test between groups), with a 5% significance level.

The two methods are compared using Bland-Altman and identity plots. The comparison between techniques for measurement of TLC is summarized using the NSD, defined as:

$$NSD = \frac{\text{std}(TLC_{Pleth} - TLC_{MB})}{\text{mean}(TLC_{Pleth} + TLC_{MB}) / 2} \quad (2)$$

To account for inherent uncertainty in both TLC_{MB} and TLC_{Pleth} measurements, the linear dependence of TLC_{Pleth} values on TLC_{MB} values was calculated using a Deming regression,²¹ with assumed equal uncertainty in both TLC_{MB} and TLC_{Pleth} . The 95% CIs for the slope were calculated as jackknife estimates as follows:

$$\pm 1.96SE \sqrt{1 + \frac{1}{N} + \frac{(TLC_{MB} - \text{mean}(TLC_{MB}))^2}{\sum (TLC_{MB} - \text{mean}(TLC_{MB}))^2}}, \quad (3)$$

where SE is the standard error of the regression and N is the sample size.

The sample size of the present study was based on detection of differences in TLC_{MB} vs TLC_{Pleth} of 0.5 L assuming an SD of 1 L for TLC measurements in the study population. The initial intent was to recruit a total of 150 participants to achieve a power of 0.8. Considering the final size of the study population ($N = 266$ after addition of the Verona site) and the observed SD for TLC measurements of 0.48 L, the study had a power of 0.92 for detecting a difference in TLC measurements between devices of 0.1 L.

TABLE 1] Anthropometric Data of the Study Population

Variable	No.	Male Sex	Female Sex	Age, y	Height, cm	Weight, kg	BMI, kg/m ²
All	266	130	136	61 ± 17	169 ± 10	75 ± 18	26 ± 5
Healthy	36	14	22	38 ± 14	170 ± 11	74 ± 15	25 ± 5
Obstructed							
All	197	95	102	64 ± 15	168 ± 10	74 ± 17	26 ± 5
Mild	110	56	54	62 ± 15	169 ± 10	74 ± 18	26 ± 5
Moderate	42	17	25	67 ± 16	167 ± 9	74 ± 16	27 ± 5
Severe	45	22	23	64 ± 13	169 ± 11	73 ± 16	25 ± 4
Restricted							
All	33	21	12	66 ± 15	171 ± 9	85 ± 29	29 ± 9
Mild	23	15	8	66 ± 15	173 ± 8	83 ± 16	28 ± 5
Moderate and severe	10	6	4	65 ± 15	170 ± 10	90 ± 48	30 ± 14

Data are presented as No. or mean ± SD.

Results

Anthropometric data of the participants are shown in [Table 1](#). A total of 266 participants were enrolled. No significant differences were found in height, sex, or age distributions among the five medical centers (with the exception of healthy participants who were significantly younger than patients). Because only one patient in the restricted group had severe obstruction, this patient's data were incorporated into a moderate and severe group.

No statistically significant differences were found in the distributions of TLC discrepancies in each center. Similarly, a leave-one-out cross-validation test showed that the overall results were not sensitive to a specific center (weighted NSD, 8.3% for cross-validation test vs 8.5% for total population). Because of the low number of participants in each severity group per center, a similar sensitivity analysis per severity was not statistically revealing. Therefore, we proceeded with a severity analysis of the overall population.

Overall Study Population

A Bland-Altman plot of all participants is shown in [Figure 5A](#) (overall NSD, 8.5%; mean discrepancy, -0.05 L). The relationship between TLC_{pleth} and TLC_{MB} values is shown in [Figure 5B](#). A tight correlation was found between TLC_{pleth} and TLC_{MB} ($R^2 = 0.89$) with a slope of 1.024, that is, no clinically meaningful difference was found from the identity line. The measured TLC differed by ≥ 1 L between the techniques in 5.6% of the total study population ($n = 15$), compatible with expectations for a Gaussian distribution given that the 95% CI of the discrepancy between TLC measurement techniques was

0.96 L. These participants with a ≥ 1 -L discrepancy in TLC measurements did not differ from the remaining study population with respect to age, sex, BMI, study center, disease type, or severity of disease.

The data were analyzed to identify instances where the final diagnosis with respect to either restriction or obstruction differed by device. First, data were analyzed from the 15 participants who demonstrated a > 1 -L difference between TLC measurements. In all but one of these individuals, both the TLC_{pleth} and TLC_{MB} agreed with respect to the diagnosis of obstruction or restriction. When the entire study population was analyzed, the final physiologic diagnosis differed by device in a total of 14 participants (five healthy participants, six obstructed participants, and three restricted participants). In 10 of these people, the TLC_{MB} characterized the physiologic pattern in accord with the clinical diagnosis.

Effect of Disease Type and Severity

A summary of results by disease type and severity is shown in [Table 2](#). The NSD between the TLC_{pleth} and TLC_{MB} measurements was 7.0% in healthy participants. For patients with obstructive disease ($n = 197$), the NSD ranged from 7.7% to 9.1%, depending on disease severity. The agreement between TLC_{MB} and TLC_{pleth} measurements was similar in groups with mild and moderate obstruction with similar 95% CIs for TLC discrepancies (mild, -0.91 to 0.39 L; moderate, -0.72 to 0.51 L). The TLC_{MB} measurements for the group with severe obstruction were less than the TLC_{pleth} measurements by an average of 0.12 L with a 40% larger spread of discrepancies (-0.82 to

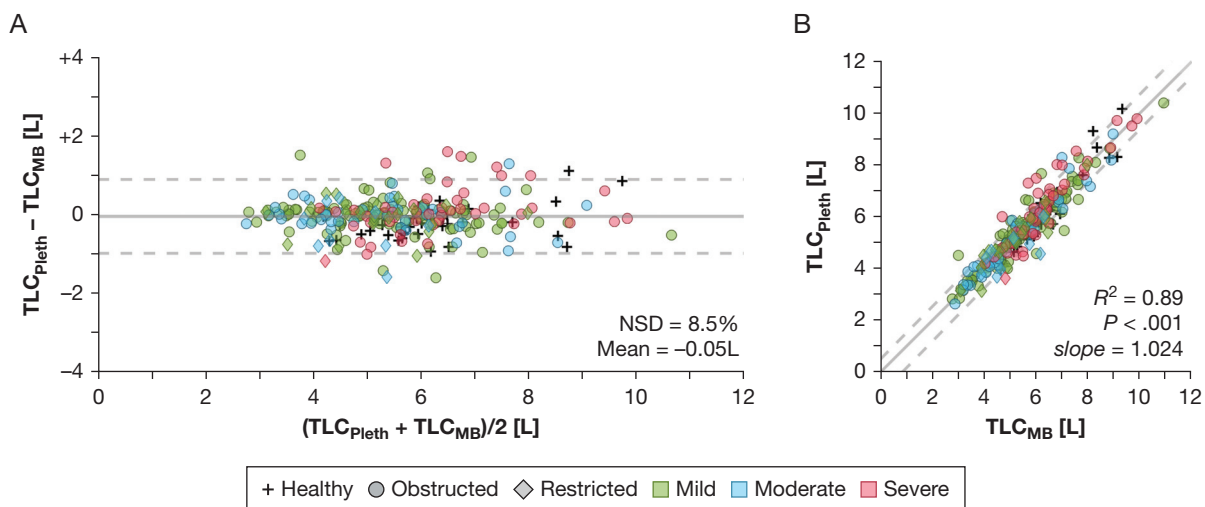


Figure 5 – Comparison of TLC_{MB} and TLC_{Pleth} for all participants in the study. A, Bland-Altman plot in which the mean discrepancy and deviations of 1.96 SD from it are shown in solid and dashed lines, respectively. The NSD and the mean discrepancy are shown. B, Identity plot showing TLC_{Pleth} vs TLC_{MB} . Solid line is the identity line. Dashed lines show 95% CIs about a linear Deming regression.²³ The R^2 , P value, and slope (1.024 ± 0.003) of the linear Deming regression also are shown. NSD = normalized root mean square difference; TLC_{MB} = total lung capacity measured by the MiniBox; TLC_{Pleth} = total lung capacity measured by plethysmography.

1.14 L), which may reflect increased heterogeneity of airway disease in these participants with severe airflow limitation; these differences were not statistically significant ($P = .19$).

Figure 6 shows a Bland-Altman plot and the relationship between TLC_{Pleth} and TLC_{MB} values in the obstructed patients. The NSD between TLC_{Pleth} and TLC_{MB} was 8.3%, with a mean discrepancy of 0.01 L. Similar to findings in the overall population, a high correlation between TLC_{Pleth} and TLC_{MB} values of obstructed patients was found ($R^2 = 0.90$) with a slope of 1.009,

that is, no clinically meaningful difference from the identity line was found.

Figure 7 shows a Bland-Altman plot and the relationship between TLC_{Pleth} and TLC_{MB} values in participants with restriction. The overall NSD between TLC_{Pleth} and TLC_{MB} was 10.3%, with a mean discrepancy of -0.18 L. In the combined moderate and severe group, the NSD was higher at 13.9% (as might be expected because of lower TLC). For all participants with restriction, a high correlation between TLC_{Pleth} and TLC_{MB} values was found ($R^2 = 0.75$), with a slope of 1.004, that is, no

TABLE 2] TLC Data Obtained by Plethysmography and MiniBox Grouped by Participant Category and Disease Severity

Variable	FVC, L	FEV ₁ , L	TLC_{Pleth} , L	TLC_{MB} , L	NSD
All	3.2 ± 1.2	2.4 ± 1.0	5.6 ± 1.4	5.7 ± 1.4	8.5
Healthy	4.3 ± 1.0	3.5 ± 0.7	6.1 ± 1.4	6.3 ± 1.2	7.0
Obstructed					
All	3.0 ± 1.1	2.2 ± 1.0	5.7 ± 1.5	5.6 ± 1.5	8.3
Mild	3.3 ± 1.1	2.5 ± 0.8	5.5 ± 1.3	5.5 ± 1.4	7.9
Moderate	2.6 ± 1.0	1.8 ± 0.8	5.3 ± 1.5	5.3 ± 1.6	7.7
Severe	2.8 ± 1.1	1.7 ± 1.0	6.5 ± 1.5	6.3 ± 1.3	9.1
Restricted					
All	2.9 ± 1.0	2.3 ± 0.9	4.9 ± 1.0	5.1 ± 1.0	10.3
Mild	3.0 ± 1.1	2.4 ± 1.0	5.2 ± 1.1	5.2 ± 1.1	7.8
Moderate and severe	2.7 ± 0.7	2.1 ± 0.6	4.4 ± 0.8	5.0 ± 0.9	13.9

Data are presented as mean ± SD or percentage. NSD = normalized root mean square difference; TLC = total lung capacity; TLC_{MB} = total lung capacity by MiniBox; TLC_{Pleth} = total lung capacity by body plethysmography.

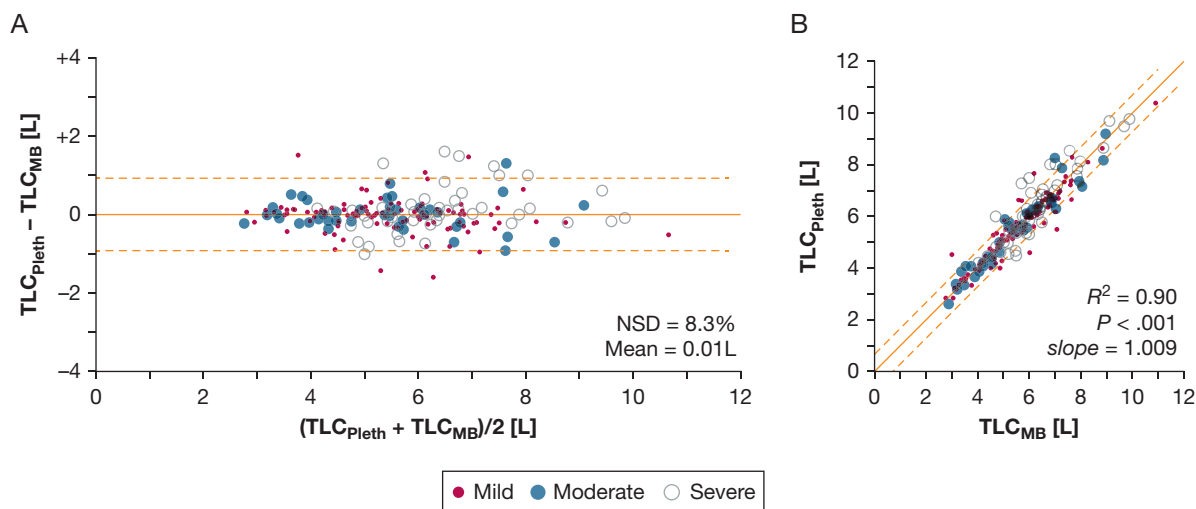


Figure 6 – Comparison of TLC_{MB} and TLC_{Pleth} for the participants with obstructive dysfunction in the study. A, Bland-Altman plot in which the mean discrepancy and deviations of 1.96 SD from it are shown in solid and dashed lines, respectively. The NSD and the mean discrepancy are shown. B, Identity plot showing TLC_{Pleth} vs TLC_{MB} . Solid line is the identity line. Dashed lines show 95% CIs about a linear Deming regression. The R^2 , P value, and slope (1.009 ± 0.003) of the linear Deming regression also are shown. NSD = normalized root mean square difference; TLC_{MB} = total lung capacity measured by the MinBox; TLC_{Pleth} = total lung capacity measured by plethysmography.

clinically meaningful difference from the identity line was found.

Discussion

Lung volume measurement is an integral part of standard physiologic assessment.¹ Knowledge of lung volumes is important in obstructive lung disease, particularly in the evaluation of hyperinflation, which is an independent predictor of all-cause and respiratory mortality.²² FRC frequently is increased in obstructive

lung disease, and TLC can increase as well, especially in patients with severe emphysema with large bullae. Increased FRC is associated with expiratory flow limitation during tidal breathing and during exercise, with resultant increase in the elastic work of breathing. Measurement of lung volumes also is essential for the evaluation of restrictive respiratory diseases.²³ Guidelines and equipment recommendations for determination of lung volumes are derived using physiologic and physics-based principles, but even the

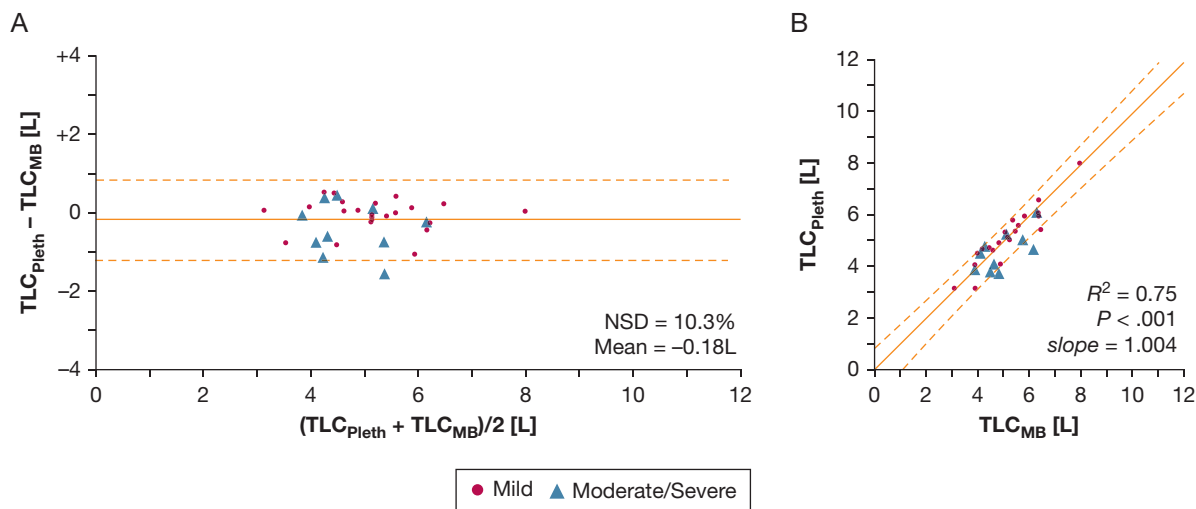


Figure 7 – Comparison of TLC_{MB} and TLC_{Pleth} for the participants with restrictive dysfunction in the study. A, Bland-Altman plot in which the mean discrepancy and deviations of 1.96 SD from it are shown in solid and dashed lines, respectively. The NSD and the mean discrepancy are shown. B, Identity plot showing TLC_{Pleth} vs TLC_{MB} . Solid line is the identity line. Dashed lines show 95% CIs about a linear Deming regression. The R^2 , P value, and slope (1.004 ± 0.031) of the linear Deming regression also are shown. NSD = normalized root mean square difference; TLC_{MB} = total lung capacity measured by the MinBox; TLC_{Pleth} = total lung capacity measured by plethysmography.

accepted plethysmography gold standard does not ensure accuracy of the measurements in patients with respiratory disease.

The choice of technique to measure lung volumes depends on availability, cost, convenience, and accuracy. The ATS/ERS Consensus Statement identifies five methods: whole body plethysmography, helium dilution, nitrogen washout, CT scanning, and chest radiography.¹⁸ The choice of an optimal system is easier in patients with pure restrictive disease because all techniques yield similar values. Accuracy becomes more difficult when assessing patients with a mixed restrictive-obstructive disorder and even more difficult in patients with obstructive airways disease. Among these standard methods, plethysmography is more accurate, but its use in the clinical setting may be limited by increased expense and difficulty obtaining measurements in patients with claustrophobia or individuals with physical disabilities. Nevertheless, plethysmography has become widely accepted globally, and therefore we chose it for comparison with the novel MiniBox measurement system.

Unlike plethysmography, determination of TLC by the MiniBox is based on inductive statistics and pattern recognition algorithms that are used to infer parameters of a mathematical model automatically. The present study demonstrated that this approach can be applied to a highly heterogeneous population of participants, yielding accurate and reproducible determination of TLC as compared with the current gold standard plethysmography technique.

Data reported here compare favorably with the only other multicenter study² that assessed TLC by a variety of techniques in a large number of healthy participants and respiratory patients. With permission from the authors,² we analyzed the raw data from the study comparing TLC_{Pleth} measurements with TLC measurements obtained by CT scanning (e-Fig 1) and by helium dilution (e-Fig 2). In our study, the NSD was 8.5% for TLC_{MB} vs TLC_{Pleth}, which compares favorably with an NSD of 11.8% and 16.6% for TLC measurements obtained by CT scanning and by helium dilution vs TLC_{Pleth} measurements, respectively.² Moreover, Figure 1 highlights that the agreement between the MiniBox and plethysmography methods is favorable as compared with other smaller studies that used numerous plethysmograph devices and numerous comparator techniques to assess TLC. These findings indicate that the MiniBox can derive absolute lung

volumes precisely in a variety of participants and patients with diseases of varying severities.

Differences in measurement standards and in the manufacturer of plethysmography devices can be a potential source of discrepancy between TLC_{Pleth} and TLC_{MB} measurements. A study recently presented at the ERS International Congress compared five plethysmography devices from the same manufacturer and found systematic differences between measured lung volumes.²⁴ In the present study, we tested a wide spread of patients from European and US centers using four different plethysmography devices. Sensitivity analyses confirmed that the agreement between TLC_{MB} and TLC_{Pleth} measurements was equivalent across plethysmography devices.

Study limitations include a relatively small sample size, particularly for some patient subgroups (eg, restrictive dysfunction), a narrow age distribution for patients with disease, and a younger healthy group. Nevertheless, the discrepancies between TLC_{MB} and TLC_{Pleth} measurements were similar across disease subgroups. In addition, this study did not assess day-to-day variability of MiniBox measurements, although in a previous study, the day-to-day variability in 26 healthy participants (expressed as a coefficient of variation) was 1.6% for TLC_{MB} compared to 3.3% for TLC_{Pleth}.¹¹ Finally, isolated TLC_{MB} values differed by 1 L compared with TLC_{Pleth} values in healthy participants and patients with respiratory diseases, consistent with real-life experience and other published studies.²⁻¹⁰ Importantly, in these people, the clinical diagnosis was aligned more closely to physiologic pattern based on TLC derived by the MiniBox than by plethysmography.

The National Heart, Lung and Blood Institute, ATS, and ERS have encouraged innovation in technologies to measure absolute lung volumes to attain improved accuracy, ease of use, and rapid assessment.²⁵ Rigorous testing is suggested to ensure that results are statistically comparable with standard techniques. In all subpopulations tested, the MiniBox performed in a manner that compared favorably with plethysmography. Moreover, the measurement of lung volumes is facilitated by reduced cost of the system as compared with plethysmography and by the ability to obtain data during tidal breathing without need for complex respiratory maneuvers. The MiniBox system is mobile and simpler to operate when compared with other lung volume measurement systems. In addition, the compact size of the MiniBox facilitates and speeds disinfection of

the hardware between patients.²⁶⁻²⁹ These considerations indicate that the MiniBox system should be considered a clinically reliable technique to obtain

measurement of lung volumes that are equivalent to plethysmography values in both healthy participants as well as those with lung disease.

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Additional information: The e-Appendix and e-Figures can be found in the Supplemental Materials section of the online article.

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Validation of a Novel Compact System for the Measurement of Lung Volumes

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e-Appendix 1.

a. Derivation of the minibox equation using Buckingham pi theory

The complexity of the human lung and the unavoidable use of empirical methods merits employing the Buckingham pi theory¹ to identify the key predictors of lung volume, given a set of physical assumptions. Here we assume that the relevant physical parameters related to instantaneous lung volume during minibox events are:

$V_L \doteq [L]$: Lung volume in units of Liter

$V_C \doteq [L]$: Container volume

$F_0 \doteq [L/sec]$: Airflow prior to the minibox event (Figure 4b in the main text)

$F_C \doteq [L/sec]$: Airflow during the minibox event (Figure 4b in the main text)

$RC \doteq [sec]$: RC timescale, set by the impedance of the lung-container system

$\alpha \doteq [1]$: heat capacity ratio of the lung divided by heat capacity ratio of the container

Since the six parameters of the system have two dimensions (volume and time), the Buckingham pi theory predicts four non-dimensional pi terms: $\frac{V_L}{V_C}$, $\frac{F_0}{F_C}$, $\frac{F_0 RC}{V_C}$, and α . Lung volume is therefore given by

$$V_L = V_C \phi\left(\frac{F_0}{F_C}, \alpha, R\right) \quad (1)$$

where ϕ is a function of the unitless parameters F_0/F_C , α and of $R \equiv \frac{F_0 RC}{V_C}$. The physical parameters $\frac{F_0}{F_C}$, α and R , as well as the specific functional form of ϕ , are determined by artificial intelligence algorithms, trained by clinical data, using plethysmography measurements of lung volume as reference^{2,3}. More information on the potential physical interpretation of Eq. (1) and on the determination of the above-mentioned physical parameters is provided in the next subsections of this Supplement. Specifically, in subsection *b* we derive an equation that relates the above-mentioned parameters to lung volume from first principles. Subsections *c* and *d* provide further information on the determination of the parameters F_0/F_C , α and R .

b. Relating lung volume to minibox events from first principles

As in traditional plethysmography, the minibox method is based upon noninvasive measurements of gas pressures and flows.^{2,3} Although the final determination of TLC by the minibox method depends upon empirical adjustments that remain proprietary, the selection of measured parameters is guided by a physical model, as described below. The physical model derived here (Eq. S17) provides insights on the relation of lung volumes to the flow interruption signal.

With these limitations in mind, we note that under isothermal conditions, the equation of state of the lungs (Boyle's law) can be written as

$$\frac{P_L}{\rho_L} = Const. \quad (S1)$$

where P denotes pressure, ρ denotes gas density, and the subscript L is used for properties of gas within the lung. Assuming adiabatic conditions in the MiniBox™ container, its equation of state can be written as

$$\frac{P_C}{\rho_C^\gamma} = \text{Const.} \quad (\text{S2})$$

where the subscript C is used for properties of the gas in the rigid container, and γ is the ratio of the specific heats of air at constant pressure and at constant volume; it is equal to 7/5 for diatomic gases, as is mostly the case for atmospheric air near the surface.

For small, time-dependent perturbations, the equation of state of gas within the lung (S1) can be written as

$$\rho_L = P_L \frac{\Delta \rho_L / \Delta t}{\Delta P_L / \Delta t} \quad (\text{S3})$$

where $\Delta \rho / \Delta t$ and $\Delta P / \Delta t$ denote the rate of change of small perturbations about ρ and P , respectively. Similarly, the equation of state of the container can be written as

$$\rho_C = P_C \gamma \frac{\Delta \rho_C / \Delta t}{\Delta P_C / \Delta t}. \quad (\text{S4})$$

Note that equations (S3) and (S4) implicitly assume differences in the equations of state of the lung and container, but uniform variations in pressure, density and temperature within the lung and within the container.

Since density is defined as the ratio of mass and volume, $\rho = m/V$, the rate of change of density can be written as

$$\frac{\Delta \rho}{\Delta t} = \frac{1}{V} \frac{\Delta m}{\Delta t} - \frac{\rho}{V} \frac{\Delta V}{\Delta t}. \quad (\text{S5})$$

For the system described in Figure 3 of the main text, in the rigid container $\Delta V_C / \Delta t = 0$. Therefore, the rate of change of density is only due to the mass flux out of the container. This mass flux is related to the flow measured at the mouth (in units of volume per second) by

$$\frac{\Delta m}{\Delta t} = -\rho_C F_C \quad (\text{S6})$$

where the minus sign indicates that the container loses mass for positive F_C . Therefore,

$$\frac{\Delta \rho_C}{\Delta t} = -\frac{\rho_C}{V_C} F_C \quad (\text{S7})$$

In the lungs, the gas density varies due to changes in both the mass and volume. The rate of mass transfer from the container to the lung is given by Eq. (S6). Further, due to muscle tension and inertia, it is assumed that the rate of change of lung volume persists for at least 20 millisecond following valve closure. Thus, F_0 is calculated as the flow immediately prior to valve closure and F_C as the flow immediately after closure (Figure 4b in main text). The limitations of this assumption and the justification for the 20 millisecond time constant are discussed in subsection *d* of this Supplement.

Applied to the lungs, Eq. (S5) then becomes,

$$\frac{\Delta \rho_L}{\Delta t} = -\frac{1}{V_L} (\rho_L F_0 - \rho_C F_C). \quad (S8)$$

Inserting Eq. (S8) into Eq. (S3) yields

$$V_L = -P_L \frac{F_0 - \frac{\rho_C}{\rho_L} F_C}{\Delta P_L / \Delta t}. \quad (S9)$$

Similarly, inserting Eq. (S7) into Eq. (S4) yields

$$V_C = -\gamma P_C \frac{F_C}{\Delta P_C / \Delta t}. \quad (S10)$$

We now turn to estimate the changes in the pressure and density of the lungs and container during minibox events. Prior to valve closure, air flows from outside the device, along the flow tube, and into the lungs (Figure 2 in the main text), driven by the pressure difference between the lungs and atmospheric pressure (P_A). This pressure difference can be written as the sum of pressure drops in the resistive elements along the path of air flow from outside the device and into the lungs. These resistive elements consist of the airway resistances of: (i) the valve (R_{Valve}), (ii) the spirometer (R_{Spiro} , i.e., of the flow meter and disposable bacterial/viral filter), and (iii) the lung (R_L). Therefore, prior to valve closure, lung and atmospheric pressure are related by

$$P_A = P_L + F_0(R_{Valve} + R_{Spiro} + R_L). \quad (S11)$$

Similarly, since the container opening is situated between the flowmeter and valve, atmospheric and container pressures are related by

$$P_A = P_C + F_0 R_{Valve}. \quad (S12)$$

Therefore, prior to valve closure,

$$P_C = P_L + F_0(R_{Spiro} + R_L) \quad (S13a)$$

which can be written as

$$\frac{P_L}{P_C} = 1 - \frac{F_0(R_{Spiro} + R_L)}{P_A + F_0 R_{Valve}}. \quad (S13b)$$

Even for severely obstructed patients ($R_L \sim 100 \text{ kPaSec/L}$), for typical flows of 1L/sec and atmospheric pressure $P_A = 10^5 \text{ kPa}$, we have $\frac{F_0(R_{Spiro} + R_L)}{P_A + F_0 R_{Valve}} \sim 1\%$. Therefore, we may assume $\frac{P_L}{P_C} \approx 1$ prior to valve closure.

It also follows that, since from Eqs. (S1) and (S2) variations in gas density are proportional to variations in pressure, we may assume $\frac{\rho_L}{\rho_C} \approx 1$ prior to valve closure.

After valve closure, the container and lung pressures are related by

$$P_C' = P_L' + F_C(R_{Spiro} + R_L) \quad (S14)$$

where ($'$) denotes values after valve closure, during the minibox event. Subtracting Eq. (S13a) from Eq. (S14) we obtain

$$\Delta P_C = \Delta P_L - (F_0 - F_C)(R_{Spiro} + R_L) \quad (S15)$$

which can be written as

$$\frac{\Delta P_C}{\Delta P_L} = 1 - \frac{(F_0 - F_C)(R_{Spiro} + R_L)}{\Delta P_L} \quad (S15b)$$

Since for inhalation ΔP_L is negative, we write Eq. (S15b) as

$$\frac{\Delta P_C}{\Delta P_L} = 1 + R \quad (\text{S15c})$$

where $R \equiv -\frac{(F_0 - F_C)(R_{Spiro} + R_L)}{\Delta P_L}$ is a positive, normalized (i.e., unitless) measure of the lung-container impedance. (Note that the normalized parameter R takes a different form than the impedance parameter presented in Eq. 1).

Now, assuming $\frac{P_L}{P_C}, \frac{\rho_L}{\rho_C} \approx 1$ and dividing Eq. (S9) by Eq. (S10) gives

$$\frac{V_L}{V_C} = \frac{1}{\gamma} \frac{F_0 - F_C}{F_C} \frac{\Delta P_C}{\Delta P_L} \quad (\text{S16})$$

Further, using Eq. (S15b), Eq. (S16) can be written as

$$V_L = \alpha V_C \frac{F_0 - F_C}{F_C} (1 + R). \quad (\text{S17})$$

where $\alpha \equiv 1/\gamma$. Thus, as predicted by Eq. (1), lung volume in the MiniBox™ can be derived from measurement of flow at the mouth from the parameters $\frac{F_0}{F_C}, \alpha$ and R . It is assumed that immediately following valve closure, the rate of lung expansion is identical as immediately prior to the event. Therefore, F_0 is calculated as the flow immediately prior to valve closure and F_C as the flow immediately after closure (see Figure 4b in main text).

c. Empirical determination of α and R

Under ideal conditions, the constant α is given by the ratio of the specific heat of air at constant volume and at constant pressure, equal to 5/7 for atmospheric air near the surface. However, the effective value of α may deviate from the theoretical value due to humidity and heat transfer that lead to deviations from isothermal conditions in the lungs and adiabatic conditions in the container. Similarly, the impedance parameter R depends on the rate of flow in addition to device characteristics and each subject's lung properties. The parameters α and R are calculated using empirical tables derived from controlled lab experiments using artificial model lungs and from a clinical study conducted in various pulmonary function laboratories^{2,3}. The empirical tables use only flow data, taken from the breathing maneuver, the minibox events, and from the spirometry. The empirical tables consist of two major factors, as described below.

The first correction is related to the validity of the assumptions of isothermal conditions in the lungs and adiabatic conditions in the container. Since the mass flux from the container to the lung carries energy, the assumption of adiabatic conditions (i.e., of energy conservation) in the container is compromised.

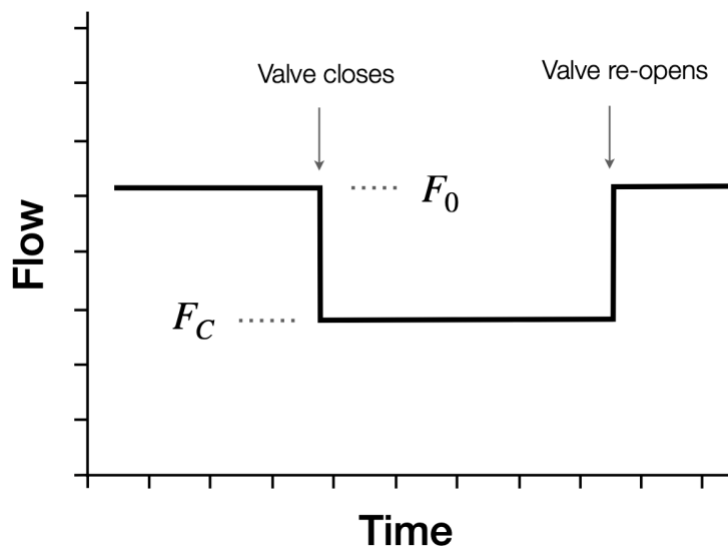
Similarly, due to the shortness of the minibox events, relaxation to isothermal conditions may not be fully achieved in the lungs, and in particular in the upper airways, thus compromising the assumption

of isothermal conditions. The deviations from adiabatic conditions in the container and from isothermal conditions in the lung were found to primarily scale with F_0 , the air flow just before the valve closes. Using controlled lab experiments with model lungs (glass bottles filled with copper wool), the dependence of α on F_0 in the MiniBox™ device was empirically determined.

In addition to the above correction, the values of α and R are determined for each subject, based on empirical tables. The empirical tables were derived using inductive statistics, based on clinical data where TLC values obtained by plethysmography were used as reference^{2,3}. To avoid sensitivity to the make of the plethysmographic device, various body plethysmography devices were used to provide the reference lung volumes. The heterogeneous population in the clinical study comprised of 434 subjects: 265 male, 169 female; 201 healthy, 170 with airflow obstruction, and 63 with mild to severe ventilatory restriction. Good day to day repeatability was found in a subgroup of 26 healthy subjects, with coefficient of variation for repeated measurements of 3.3% for TLC derived from plethysmography versus 1.6% for TLC provided by the MiniBox™.

d. Justification of the 20 millisecond interval

In the idealized case where the valve instantly closes, the lungs expand at the same rate before and after valve closure, and the lung-container system efficiently equilibrates, the flow signal during a minibox event will look like the depiction shown below:



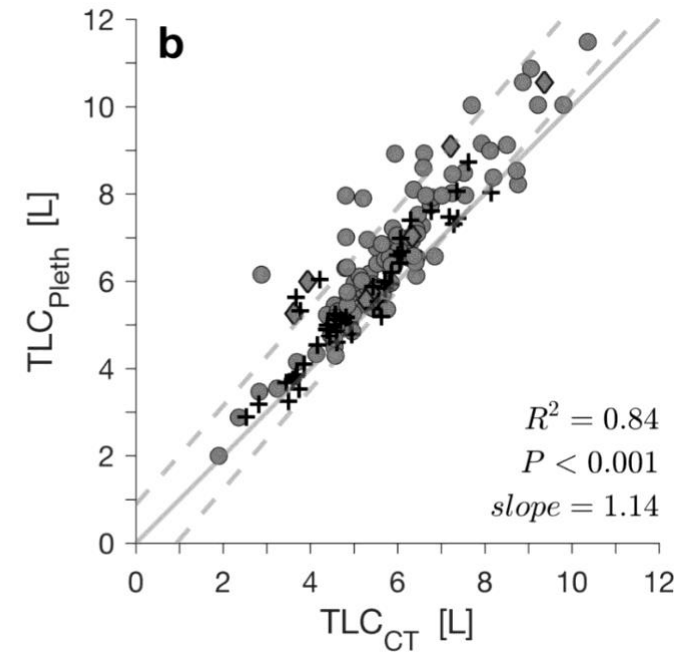
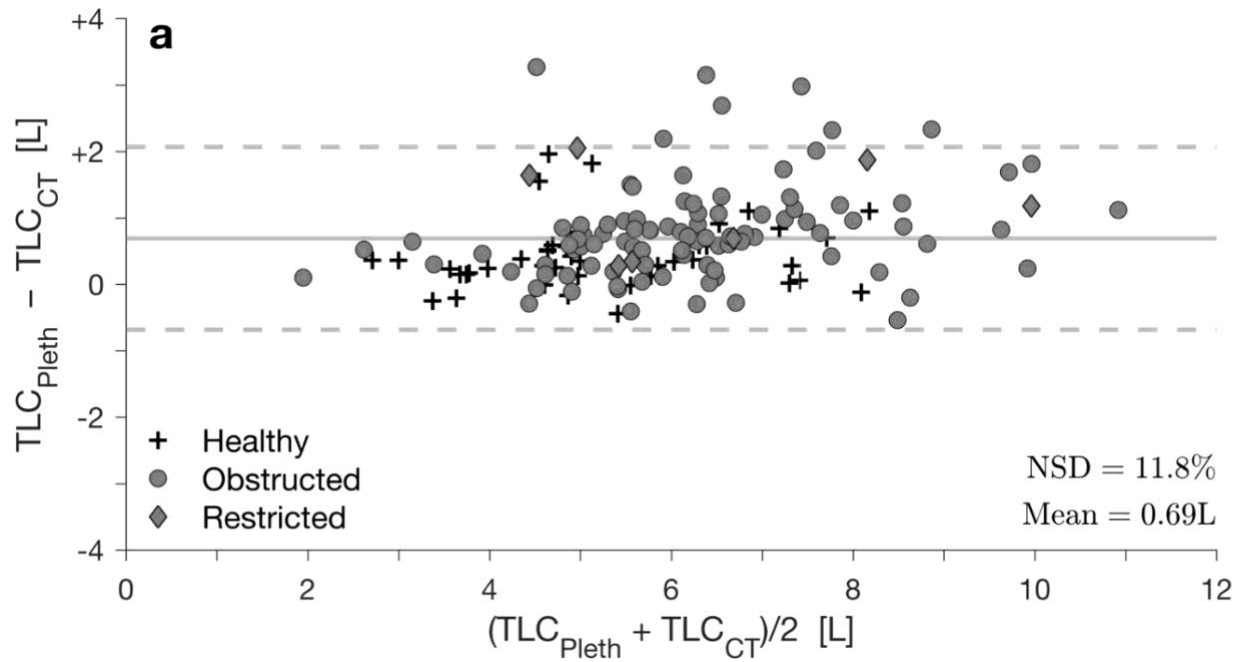
An illustration of airflow during a minibox event under ideal conditions of constant lung expansion rate. Following valve closure, airflow at the mouth drops from F_0 to F_C ; after the valve reopens, the flow level returns to F_0 .

As depicted in Figure 4b of the main text, minibox events in human subjects show the predicted step-like drop from F_0 to F_c after valve closure, followed by a gradual decrease in the flow (i.e., it deviates from the theoretical prediction shown above). Extensive measurements of human subjects indicate that the time interval during which the rate of lung expansion can be assumed constant is at least 20 milliseconds after valve closure, which is the interval used in the MiniBox™ device. This time interval is shorter than the typical time scales for equilibrium in the lungs suggesting that at 20 milliseconds the system has not fully equilibrated. Nevertheless, calculation of F_c using this time constant was empirically found to provide a repeatable and robust measure of flow variation, that predicts lung volume.

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e-Figure 1: TLC_{Pleth} and TLC_{CT} data obtained by O'Donnell et al. are plotted in Bland Altman and Identity plots. The graphs include an additional 17 subjects (provided by personal communication) who were not included in the original publication. The normalized root-mean-squares difference (NSD) and the mean discrepancy are shown. In the identity plots, the solid line is the identity line and dashed lines show 95% confidence intervals about a linear Deming regression. The R^2 , p -value and the slope (1.14 ± 0.01) of the linear Deming regression are also shown.



e-Figure 2: TLC_{Pleth} and TLC_{He} data obtained by O'Donnell et al. are plotted in Bland Altman and Identity plots. The graphs include an additional 17 subjects (provided by personal communication) who were not included in the original publication. The normalized root-mean-squares difference (NSD) and the mean discrepancy are shown. In the identity plots, the solid line is the identity line and dashed lines show 95% confidence intervals about a linear Deming regression. The R^2 , p -value and the slope (1.24 ± 0.01) of the linear Deming regression are also shown.

