Methods for Measuring Lung Volumes: Is There a Better One?

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Key Words

Lung volume management · Ventilatory defects

Abstract

Background: Accurate measurement of lung volumes is of paramount importance to establish the presence of ventilatory defects and give insights for diagnostic and/or therapeutic purposes. **Objectives:** It was the aim of this study to measure lung volumes in subjects with respiratory disorders and in normal controls by 3 different techniques (plethysmographic, dilutional and radiographic methods), in an attempt to clarify the role of each of them in performing such a task, without any presumptive 'a priori' superiority of one method above others. **Patients and Methods:** In different groups of subjects with obstructive and restrictive ventilatory defects and in a normal control group, total lung capacity, functional residual capacity (FRC) and residual volume were measured by body plethysmography, multi-breath helium (He) dilution and radiographic CT scan method with spirometric gating. **Results:** The 3 methods gave comparable results in normal subjects and in patients with a restrictive defect. In patients with an obstructive defect, CT scan and plethysmography showed similar lung volumes, while on average significantly lower lung volumes were obtained with the He

dilution technique. Taking into account that the He dilution technique does primarily measure FRC during tidal breathing, our data suggest that in some patients with an obstructive defect, a number of small airways can be functionally closed at end-expiratory lung volume, preventing He to reach the lung regions subserved by these airways. **Conclusion:** In all circumstances, both CT scan with spirometric gating and plethysmographic methods provide similar values of lung volumes. In contrast, the He dilution method can measure lower lung volumes in some patients with chronic airflow obstruction.

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Introduction

Accurate measurement of lung volumes is of paramount importance to establish the presence of ventilatory defects [1] and gives useful insights for diagnostic and/or therapeutic purposes [2]. In fact, the determination of forced expiratory volume in 1 s (FEV₁) during a single spirometry can hardly establish the exact nature and severity of the ventilatory defect (obstructive, restrictive or mixed) in the absence of accurate measurements of lung volumes [3]. Moreover, knowledge of lung vol-

ume changes is crucial to follow the natural history of many obstructive and restrictive respiratory diseases and their response to different treatments [4, 5]. Some lung volumes, however, are not directly measurable, and different indirect methods have been developed to determine them. Essentially, two methods have been employed in the respiratory function labs. One implies the use of a body plethysmograph that can measure the volume of the compressible air inside the thorax (normally the same present in the lung) in accordance with the Boyle-Mariotte law [6]. The other entails the multi-breath dilution technique using gases either resident, such as nitrogen that is almost completely washed out from the lungs by inspiring pure oxygen in an open circuit, or external, such as helium (He) that is breathed in a closed circuit until its equilibrium is reached between the lung and the spirometer [7, 8]. End-expiratory lung volume, usually corresponding to functional residual capacity (FRC), is measured by both methods, and residual volume (RV) and total lung capacity (TLC) are calculated subsequently. Recently, however, the volume-rendering technique of chest computed tomography (CT scan) has allowed a volumetric reconstruction of the air content of the lung after full inspiration, directly measuring supine TLC [9]. In the past, these methods have been assessed in large cohorts of subjects, considering the radiographic method (lung CT scan) as a reference for comparison [10]. This assumption that can be confuted if several variables of interest are not carefully checked [11] has generated controversial interpretation regarding the accuracy of the above-mentioned methods for measuring lung volumes (essentially TLC) [10, 11]. The aim of our work was to compare lung volume measurements in patients with various respiratory disorders and healthy subjects obtained by 3 different methods (namely plethysmographic, dilutional and radiographic methods). Thus, as far as possible, we tried to control all the relevant confounding variables in an attempt to clarify the role of each technique in performing such a task, without any presumptive 'a priori' superiority of one method above others.

Patients and Methods

Twenty consecutive patients with an obstructive ventilatory defect (either suffering from chronic obstructive pulmonary disease or chronic asthma), 7 consecutive patients with a restrictive ventilatory defect (3 suffering from interstitial lung diseases, 2 from kyphoscoliosis and 2 with pleural diseases) and 10 consecutive normal subjects who had to undergo a CT scan for different reasons (chronic cough, hemoptysis and pulmonary nodules), all

in stable condition, were studied on the same day after adequate pharmacological washout, if necessary. Specifically, long-acting bronchodilators (both antimuscarinic and β_2 -agonist drugs) were withdrawn 48 h and theophylline 24 h before starting the protocol. Patients with concurrent cardiac, neuromuscular, endocrine and mental diseases were excluded from the study. Each subject and patient signed written informed consent according to the protocol approved by the local institutional review board.

In the morning, always following a prefixed sequence, each subject wearing a nose clip performed spirometry to obtain upright expiratory vital capacity (VC), maximal flow-volume curve and measurement of lung volumes, before using body plethysmography and then the He dilution multi-breath technique in the seated position. Pulmonary function tests were performed with Biomedin Instruments, Padova, Italy. For plethysmograph-obtained lung volumes, cheeks were supported and a painting frequency of about 0.7 Hz was chosen [12]. Three acceptable tracings of mouth pressure versus box volume changes were averaged to achieve a final measurement of FRC, after correction for baseline end-expiratory lung volume. The body plethysmograph was a pressure-constant plethysmograph (Biomedin). For He-obtained lung volumes, the end of the test was determined when the He concentration did not change ($<0.02\%$ for 30 s) during rebreathing and after a full expiration towards RV. The mean FRC value obtained by two acceptable maneuvers was considered to achieve the final FRC measurement. The closed-circuit and He rapid analyzer was built by Biomedin. Expiratory VC was then measured 10 min after assuming the supine position. Immediately thereafter, the subjects were transferred to the radiology unit of our hospital and, after adequate instruction, their supine TLC was measured by CT scan with spirometric gating using a portable spirometer, which had previously been carefully calibrated (Biomedin). After full inspiration, a manually driven shutter valve, assembled in series with a spirometer, was closed to assure no air losses from the mouth during acquisition time.

CT examinations were performed on a multidetector CT scanner (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany) with the following parameters: detector collimation, 128×0.6 mm; beam pitch, 1.2; rotation time, 0.5 s; tube voltage, 120 kVp; tube current, 80 mA_{eff}; care dose, off, and matrix, 512×512 .

Acquisition, extended from the hard palate to the lung base, was performed in inspiratory apnea under spirometric control of the lung volume. The average scanning time was 5.7 s. Axial images were reconstructed as 1-mm-thick sections, using a sharp reconstruction algorithm (B60f). This data set was transferred from the CT scanner to a thin client (Aquarius iNtuition, Tera-Recon Inc., Foster City, Calif., USA). TLC,CT (including anatomic dead space) was calculated using a dedicated software package for lung analysis (SAT module) with a semiautomated 3D volume-based region-growing algorithm. A region-growing algorithm is a simple image segmentation method that starts by selecting a set of pixels (called seed points) into the images and groups the neighboring pixels based on a membership criterion (i.e. pixel density). The seed points then grow into larger regions until all pixels that meet this criterion are included. The segmentation process is completed when the entire lung volume and the anatomic dead space were correctly segmented. At the end of the process, the measurement of the segmented volume (i.e. TLC,CT) is shown in cubic centimeters and then converted to liters (fig. 1). The ex-

Fig. 1. Three-dimensional view of the segmented lung volume and anatomical dead space (colored in green) of a representative normal subject at full inspiration and its measurement by CT scan in cubic centimeters (TLC,CT; color refers to the online version only).

pert chest radiologist (A.B.) was unaware of the spirometric functional data, and the final results were compared at the end of the study.

With the plethysmographic and dilutional techniques, lung volumes were obtained in the seated position, measuring FRC first and then, using expiratory reserve volume and VC, calculating RV and TLC, respectively. Since TLC with the radiographic (CT scan) method (TLC,CT) was measured in the supine position, to compare TLC among the 3 methods, we recalculated either plethysmographic and dilutional supine TLC by subtracting the difference between VC obtained in the seated and supine position to TLC previously calculated in the seated position with both methods: $TLC_{pleth\ supine} = TLC_{pleth} - (VC_{seated} - VC_{supine})$ and $TLC_{He\ supine} = TLC_{He} - (VC_{seated} - VC_{supine})$. On the other hand, $TLC_{CT\ 'seated'}$ was recalculated by adding the difference between VC obtained in the seated and supine position to TLC_{CT} previously measured in the supine position: $TLC_{CT\ seated} = TLC_{CT} + (VC_{seated} - VC_{supine})$, by assuming no change in RV with the recumbent position. Radiographic RV and FRC were calculated from the seated TCL_{CT} by using VC to obtain RV_{CT} and then by adding expiratory reserve volume to RV_{CT} to obtain FRC_{CT} . The acceptability and repeatability criteria of pulmonary function testing that we used were those proposed by the ERS/ATS guidelines [2, 3].

Table 1. Anthropometric and functional parameters of controls and patients with an obstructive (obstructed) or restrictive (restricted) ventilatory defect

	Controls	Obstructed	Restricted
Subjects, n	10	20	7
Sex, M/F	10/0	16/4	6/1
Age, years	56.7±10.5	70.4±8.5**	65.7±12.7
Weight, kg	82.2±15.2	68.8±12.7*	82.2±11.3
Height, cm	1.74±0.1	1.64±0.1***	1.67±0.1 [§]
BMI	27.0±4.2	25.7±3.9	29.40±2.9
VC, l	5.11±0.79	3.10±0.96***	2.54±0.58 ^{§§}
VC, % pred.	116.6±6.7	95.8±21.5*, [‡]	72.5±16.5 ^{§§}
VC supine, l	4.94±0.68	2.90±0.99***	2.32±0.55 ^{§§}
ΔVC seated/supine, l	0.17±0.15	0.20±0.22	0.22±0.11
ERV, l	1.60±0.36	1.18±0.54	0.75±0.22 [§]
FVC, l	4.88±0.77	2.69±0.99***	2.37±0.55 ^{§§}
FVC, % pred.	115.9±7.5	85.6±23.2***	71.0±19.3 ^{§§}
FEV ₁ , l	3.67±0.69	1.16±0.63***	1.80±0.35 ^{§§}
FEV ₁ , % pred.	109.4±9.1	46.9±20.6***, [‡]	69.3±21.3 ^{§§}
FEV ₁ /VC, %	71.6±4.4	36.1±9.7***, ^{‡‡}	71.8±9.9
FEV ₁ /VC, % pred.	92.9±5.0***	48.3±13.1***, ^{‡‡}	95.3±14.9

Values are the mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus controls. [§] $p < 0.01$; ^{§§} $p < 0.001$ versus controls. [‡] $p < 0.05$; ^{‡‡} $p < 0.001$ versus restricted.

Statistical Analysis

Differences among techniques were assessed by analysis of variance, with technique and ventilatory defects as fixed factors. The Mann-Whitney test was used for pairwise post hoc comparison of within-group differences in lung volumes according to the measurement technique. The Bland-Altman test was used to assess the agreement of the different methods for measuring various lung volumes [13]. A p value < 0.05 was considered significant.

Results

The anthropometric and functional characteristics of the patients and controls are shown in table 1. The patients with both obstructive and restrictive ventilatory defects were significantly older than the normal subjects who were in turn taller than those in the other two groups. As expected, FEV₁ values (as % predicted) were reduced either in obstructed or restricted patients as compared with controls, while VC and FVC (as % predicted) were significantly lower in patients with a restrictive ventila-

Fig. 2. The TLC, FRC and RV values measured in the seated position are shown in the 3 groups of subjects for the 3 different methods; in this case, the lung volumes obtained with the radiographic method were recalculated. The TLC values measured in the supine position are also shown; in this case, TLC obtained with the

plethysmographic and dilution methods were recalculated (black bars = radiographic method; white bars = plethysmographic method; gray bars = He dilution method). * $p < 0.05$ versus both radiographic and plethysmographic method.

Table 2. Differences (mean $\pm$ SD) in TLC among the 3 methods in 3 groups of subjects

	Controls	Obstructed	Restricted
TLC,CT – TLC,pleth, l	0.11 $\pm$ 0.26	0.07 $\pm$ 0.42	0.08 $\pm$ 0.38
TLC,CT – TLC,He, l	0.19 $\pm$ 0.36	1.32 $\pm$ 1.54	0.21 $\pm$ 0.38
TLC,pleth – TLC,He, l	0.09 $\pm$ 0.16	1.25 $\pm$ 1.62	0.14 $\pm$ 0.22

tory defect compared with controls and obstructed patients. The difference between seated and supine VC was small, comparable to those values typically reported, and it was similar among the groups.

TLC both in the seated and supine position was displayed in absolute values for the 3 methods in the 3 groups of subjects in figure 2. The above-mentioned anthropometric differences explain why TLC was apparently similar between obstructed and control subjects. The FRC and

RV values obtained in the seated position are also shown in figure 2.

The Bland-Altman plots concerning TLC for the different methods are shown in normal subjects and in patients with a restrictive ventilatory defect in figure 3a and in patients with an obstructive ventilatory defect in figure 3b. In both normal subjects and patients with a restrictive defect, there was a very good agreement among the different methods (table 2). In contrast, while a good agreement was observed between radiographic and plethysmographic methods, also for patients with an obstructive defect, throughout the range of TLC values, in these patients, the dilutional method showed lower TLC values than the two other methods (table 2). Coefficients of determination among TLC values obtained with different methods of lung volume measurement in controls and in both restricted and obstructed patients are displayed in table 3. The relationship between TLC,pleth and TLC,CT is displayed in figure 4a for controls and in figure 4b for both

Fig. 3. a Bland-Altman plots for TLC are depicted in controls (white circles) and patients with a restrictive ventilatory defect (black squares) for the 3 different methods of lung volume measurement. **b** Bland-Altman plots for TLC are depicted in patients with an obstructive ventilatory defect (black diamonds) for the 3 different methods of lung volume measurement.

Table 3. Coefficients of determination among TLC obtained with different methods of lung volume measurement

	Controls	Obstructed	Restricted
TLC,pleth (l) vs. TLC,CT (l)	$r^2 = 0.98$; $p < 0.01$	$r^2 = 0.97$; $p < 0.01$	$r^2 = 0.98$; $p < 0.01$
TLC,pleth (l) vs. TLC,He (l)	$r^2 = 0.99$; $p < 0.01$	$r^2 = 0.62$; $p < 0.01$	$r^2 = 0.98$; $p < 0.01$
TLC,He (l) vs. TLC,CT (l)	$r^2 = 0.96$; $p < 0.01$	$r^2 = 0.66$; $p < 0.01$	$r^2 = 0.97$; $p < 0.01$

Fig. 4. The relationship between TLC values measured by CT scan and body plethysmography in controls (**a**) and both restricted and obstructed patients (**b**) is displayed together with the identity line. Note the remarkable similarity of TLC obtained with these two methods.

obstructed and restricted patients, showing a very high correlation with a linearity not dissimilar from the identity line.

Discussion

The results we obtained show very clearly that in control subjects with normal pulmonary function testing, identical TLC, FRC and RV values were measured by using all 3 methods. Actually, in this case, the differences were trivial (few milliliters), and these techniques were essentially interchangeable. Similar results were found in the presence of pure ventilatory restrictive defects, independently from the underlying cause (pulmonary, pleural or chest wall diseases) among the different methods. In these patients, however, the 95% limits of agreement of TLC,He and TLC,pleth were smaller than the other limits including TLC,CT. This seems essentially due to two outlier values (one pertinent to one restricted patient and the other one to a control subject) in the measurement of TLC,CT, making the difference compared with the other methods greater than 400 ml.

When an obstructive ventilatory defect occurred, the lung volume values were similar for the plethysmographic and radiographic methods, making them largely comparable. In contrast, significantly reduced lung volumes were found in average for the He dilution technique as compared with the others (fig. 2). The mean value of the

difference between TLC,He versus TLC,pleth and TLC,He versus TLC,CT in the obstructed patients is not a bias, but reflects the fact that in several of those patients the TLC measurements obtained by the dilutional method are lower, albeit not wrong (fig. 3b). Actually, if the gas tracer during the multi-breath technique cannot reach some lung regions because they are served by small airways functionally closed at end-expiratory lung volume (i.e. FRC), this lung volume and the others subsequently computed (i.e. RV and TLC) will be necessarily smaller. We have to point out that this difference was not present in all cases of chronic airflow obstruction, but presumably only when functional closure of some small airways occurs during tidal breathing (i.e. at FRC) [14, 15].

As a general comment, we would like to emphasize the concept that there is no superiority of one method over the others, because it is a matter of appropriateness rather than accuracy. In fact, each method quantifies the lung volumes by measuring different things (the compressible air in the thorax, the air in the lung accessible by a gas tracer and the pixels with radiological air density). In some pathophysiological conditions overlaps are measured, in other conditions this does not happen.

Several strengths can be claimed in this study. For each subject, lung volumes were measured sequentially with the 3 methods on the same morning at the same institution and using the same technologies. This eliminates any potential error due to different instrumentations and technical procedures, and different time intervals be-

tween the lung volume measurements with different methods.

In addition, to our knowledge, this is the first study using both spirometry gating and shutter occlusion during CT scan measurement of TLC in the supine position. This approach has to be underlined because it allows a strict control of complete lung inflation avoiding any inadvertent air loss from the subject during the CT scan acquisition time. Moreover, the anatomical dead space was calculated during CT scan measurement of TLC. This might partially explain why in previous studies, in contrast with our results, CT scan values of TLC were significantly lower than those obtained by body plethysmography [10].

Finally, to compare the lung volumes obtained with these 3 methods, accurate measurements of VC, even in the supine position, were performed in each subject to allow the correction needed because of different body position (supine vs. seated). In fact, TLC measured during recumbency, as required by CT scan, is intrinsically lower, mainly because a greater amount of blood is conveyed to the thorax following the posture-related increase in venous return from the legs, thus reducing the available air volume [16, 17].

During lung volume measurement with the body plethysmograph, we carefully adopted a low panting frequency and a strong support of the cheeks and chin that tend to eliminate the damping and/or delay between the alveolar pressure and mouth pressure changes potentially occurring in the presence of airflow obstruction [11]. Reduced and/or delayed mouth pressure swings as compared with the alveolar ones during compression and decompression maneuvers against a closed shutter have been invoked to support the idea that body plethysmography induces artifactual increase in lung volumes in patients with chronic obstructive pulmonary disease and chronic or acute asthma [18, 19]. In our cases, similar results were obtained with CT scan and body plethysmography in patients suffering from an obstructive defect, suggesting that following an adequate approach, the lung volumes measured by a body plethysmograph are

not systematically overestimated and may be accurate also in patients with high airway resistance.

Therefore, as far as possible, we tried to control any potential source of error of measurement inherent to the different procedures related to the different methods in order to carefully compare the respective values of lung volumes obtained by each of them. It must be stressed, however, that the CT scan lung volumes were measured only once, whereas the values of the lung volumes obtained with the other methods were the mean of at least two acceptable measurements.

On the other hand, a limitation of the study could be the small number of the subjects in each group. However, each measurement was made at our best, and the range of airflow obstruction severity, according to baseline FEV₁ values as % predicted, was very large in the group with obstructive defects, leaving us very confident that these results were not obtained simply by chance.

In conclusion, both radiographic (i.e. CT scan with spirometric gating) and plethysmographic methods provide similar values of lung volumes in all circumstances, suggesting that body plethysmography, when performed with a standardized procedure, does not overestimate TLC, FRC and RV even in the presence of airflow obstruction. In contrast, the He dilution method can measure lower lung volumes in some patients with airflow obstruction. Actually, these methods are complementary because the difference in FRC between the He dilution technique and body plethysmography (or CT scan) eventually found in obstructed patients might be very useful to quantify the amount of lung volume that is not appropriately ventilated due to the functional closure of small airways at end-expiratory lung volume.

Financial Disclosure and Conflicts of Interest

All authors declare no conflicts of interest concerning the content of this study.

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