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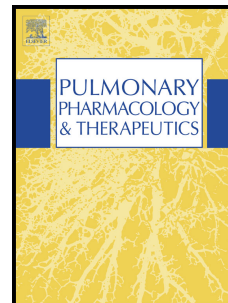
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**A pilot comparison of helium dilution and
plethysmographic lung volumes to assess the impact
of a long-acting bronchodilator on lung
hyperinflation in COPD**

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Summary

Background: Currently, two methods for measuring TLC, RV, and FRC are used in clinical pulmonary function laboratories: body plethysmography and helium dilution. However, these methods are not interchangeable. In moderate-to-severe airflow obstruction, dilution method tends to underestimate and body plethysmography tends to overestimate RV.

Purpose In 21 patients suffering from COPD (basal FEV₁: 56.69 ± 13.64), we investigated whether the two methods of measuring FRC and RV could respond differently to a 2-week treatment with tiotropium 18 µg/day.

Main results: Tiotropium induced a significant increase in FEV₁ and FVC but not in IC. At baseline, FRC_{pleth}, RV_{pleth} and TLC_{pleth} were higher than FRC_{He}, RV_{He} and TLC_{He}. At the end of the study FRC_{pleth}, RV_{pleth} and TLC_{pleth} decreased and FRC_{He}, RV_{He} and TLC_{He} increased but only changes in FRC_{pleth} and RV_{pleth} were statistically significant.

Conclusion: The use of body plethysmography seems to be more appropriate in clinical trials aimed at assessing the impact of a therapeutic procedure in patients with COPD and lung hyperinflation.

Abbreviations

COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; FRC: functional residual capacity; FVC: forced vital capacity; IC: inspiratory capacity; RV: residual volume; RV_{He}: RV measured by multibreath helium equilibration; RV_{pleth}: RV measured by plethysmography; TLC: total lung capacity; TLC_{He}: TLC measured by multibreath helium equilibration; TLC_{pleth}: TLC measured by plethysmography.

Key words

Chronic obstructive pulmonary disease; lung hyperinflation; methods for measuring TLC, RV and FRC; body plethysmography; helium dilution; tiotropium.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive airflow limitation along with changes in lung compliance and elastic recoil that are manifested by hyperinflation [1]. Lung hyperinflation, defined as an abnormal increase in the volume of air remaining in the lungs at the end of spontaneous expiration, is present in COPD because of the effects of increased lung compliance as a result of the permanently destructive changes of emphysema and expiratory flow limitation [2]. It has been thought to be an important contributor to dyspnoea and exercise limitation [2]. Therefore, therapeutic interventions that reduce or delay the development of lung hyperinflation, both at rest or during exercise, can significantly prolong exercise tolerance and reduce exertional breathlessness in patients with COPD [3].

Since lung hyperinflation and its reduction in response to a bronchodilator are not reflected in routine spirometry in hyperinflated patients, functional residual capacity (FRC) and residual volume (RV) are useful measures for the identification of a therapeutic response that may not be determined from measuring forced expiratory volume in one second (FEV_1) [4]. Inspiratory capacity (IC), the maximum volume of gas that can be inspired from end-tidal expiration, which is the difference between total lung capacity (TLC) and FRC, could also be considered, although measuring IC after a pharmacological intervention without plethysmographic determination of the static lung volumes may not be an adequate reflection of the underlying changes in these volumes [4].

Currently, two methods for measuring FRC, RV, and TLC are used in clinical pulmonary function laboratories: body plethysmography and helium dilution [5]. Either method can be used, provided the equipment meets the standard requirements [5], although the former is considered the gold standard [6]. Nonetheless, many researchers question the acceptance of body plethysmography as the best method because it can overestimate lung volumes in the presence of airway obstruction [7]. On the other side, helium

dilution underestimates FRC, RV, and TLC in the presence of airways obstruction because helium does not mix with the alveolar gas in the unventilated portion of the lung [8].

Whatever the case may be, the recent document of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force on "Outcomes for COPD pharmacological trials: from lung function to biomarkers" [4] has clearly stated that helium dilution and body plethysmography are not interchangeable when a pharmacological intervention is examined, but, to the best of our knowledge, there are no published studies that have compared helium dilution and plethysmographic lung volumes to assess the impact of a bronchodilator on lung hyperinflation in COPD. In particular, there is no data that tells us whether it is preferable to determine FRC, RV, and TLC with the helium dilution method rather than with body plethysmography when we wish to assess the impact of the reduction in lung hyperinflation on dyspnea and exercise limitation.

Because of this gap in the published literature, we have compared the two methods of measuring TLC, RV, and FRC when the impact of a bronchodilator is assessed in hyperinflated COPD patients.

Methods

We enrolled 21 selected patients suffering from stable COPD, as defined by the ATS/ERS recommendations [9], but with clear signs of functional lung hyperinflation. Patients were required to meet the following spirometric and static lung volume criteria: $FEV_1 > 30\%$ but $< 65\%$ of predicted values, an $FEV_1/\text{forced vital capacity (FVC)}$ ratio $< 70\%$, and lung hyperinflation demonstrated by $FRC \geq 120\%$ of predicted value. Patients with a history of asthma, allergic rhinitis or atopy, an elevated total eosinophil count, a recent respiratory tract infection or under a regular treatment with theophylline were excluded. Table 1 illustrates basic anthropometric data of the studied population. Eleven patients were current smokers and 10 ex-smokers. All trial procedures were conducted according to the Declaration of Helsinki.

Enrolled subjects were allocated to a 2-week run-in period during which patients were required to discontinue all previous inhaled anticholinergic and long-acting β -agonist use, but they were allowed to take salbutamol for control of symptoms and an inhaled corticosteroid if already used. If at visit 2 patients still fitted with the mentioned criteria for inclusion and exclusion, they were included in the study and began to receive a daily morning inhalation of 18 μ g tiotropium HandiHaler[®] (Boehringer Ingelheim, Milan, Italy) for 14 days.

Before and at the end of the 2-week treatment (all determinations were made 24 hours after the inhalation of the last dose of the drug), subjects performed a variety of pulmonary function studies (e.g., spirometry obtained by means of a pneumotachograph, and lung volumes measured by multibreath helium equilibration and body plethysmography).

Pulmonary function testing was performed with automated equipment (Master Screen Body PFT Jaeger, Würzburg, Germany) using the current recommendations of the ATS/ERS Task Force on standardisation of pulmonary function tests [5, 10, 11].

Results

All patients completed the study treatment period without the occurrence of any side effect worthy of reporting.

Two-week treatment with tiotropium induced significant changes in resting lung function measurements. FEV₁ increased significantly by a mean of 0.143 L (95% CI: 0.054 – 0.232, p=0.0031). Also FVC improved significantly (0.246 L, 95% CI: 0.07 – 0.420, p=0.0081), which is consistent with a volume recruitment, and in effect we recorded an increase in IC that, however, was not significant (0.184 L, 95% CI: -0.034 – 0.403, p = 0.094) (Figure 1).

As expected, FRC_{pleth} and RV_{pleth} measured by plethysmography fell significantly (-0.309; 95% CI: -0.156 – -0.463, p=0.0004; and -0.311 L; 95% CI: -0.093 – -0.528, p=0.0072, respectively), while FRC (FRC_{He}) and RV (RV_{He}) measured by multibreath helium equilibration increased (0.218 L, 95% CI: -0.109 – -0.544; 0.166 L, 95% CI: -0.105 – 0.437, respectively) but the

changes induced by tiotropium were not significant ($p=0.1801$, and $p=0.2151$, respectively) (Figures 2 and 3).

Changes in FRC_{pleth} and RV_{pleth} were not followed by a significant decrease in TLC measured by plethysmography (TLC_{pleth}) (-0.125 L, 95% CI: $-0.285 - 0.035$, $p=0.1183$) (Figure 4). Conversely, changes in FRC_{He} and RV_{He} were accompanied by an increase in the TLC measured by multibreath helium equilibration (TLC_{He}) (0.225 L, 95% CI: $-0.167 - 0.616$). This change was consistent, but not statistically significant ($p=0.2453$) (Figure 3).

The changes in FRC_{pleth} correlated significantly with those in IC ($r^2=0.4111$, $p=0.0017$), but not with those in FEV_1 ($r^2=0.01462$, $p=0.6016$) and FVC ($r^2=0.02908$, $p=0.4599$), whereas changes in FRC_{He} did not correlate with changes in FEV_1 ($r^2=0.01751$, $p=0.5674$) and FVC ($r^2=0.01487$, $p=0.5985$), and also with those in IC ($r^2=0.05165$, $p=0.3218$).

The changes in RV_{pleth} correlated significantly with those in FVC ($r^2=0.2272$, $p=0.0289$), but not with those in FEV_1 ($r^2=0.1260$, $p=0.1144$) and IC ($r^2=0.02831$, $p=0.4660$), whereas changes in FRC_{He} did not correlate with changes in FEV_1 ($r^2=0.001440$, $p=0.8703$), FVC ($r^2=0.0004430$, $p=0.9278$), and IC ($r^2=0.1160$, $p=0.1309$).

Discussion

Our data confirm that in patients with COPD and lung hyperinflation, the multiple breath helium dilution technique method underestimates lung volumes [6], while body plethysmography overestimates them [5]. They also show that helium dilution provides TLC values lower than those obtained with body plethysmography, although there is a trend for a smaller difference that follows the reduction of bronchial obstruction induced by a bronchodilator. We know that the relatively small sample of patients enrolled in this study could be regarded as a limitation, but it must be considered that this study was conducted in a single centre as a pilot investigative trial. In any case, the documentation that only FRC_{pleth} and RV_{pleth} significantly changed after a pharmacological intervention clearly indicate that body plethysmography is

always preferable to helium dilution technique when we wish to measure the impact of a bronchodilator on lung hyperinflation.

Our data show that the changes in IC correlated significantly with changes in FRC_{pleth} . Therefore, we would suggest that change in IC before and after regular treatment with a bronchodilator is a strong surrogate for the changes in FRC_{pleth} . This our opinion fits with the documentation that acute interventions, in which TLC can be assumed to be constant (in our study changes in FRC_{pleth} were not followed by a significant decrease in TLC_{pleth}), changes in IC are a good surrogate for changes in FRC_{pleth} [4]. We must stress, however, that we have enrolled patients with lung hyperinflation documented by a FRC_{pleth} value $\geq 120\%$ of predicted normal, without taking into account the value of basal IC. This may have been a bias because stratification taking into account the baseline IC value seems to be essential. In fact, in patients with reduced baseline IC, the bronchodilators elicit a greater increase of IC than in the patients with baseline IC within normal limits [12].

It should be highlighted that in our study all determinations to evaluate the impact of tiotropium treatment were made 24 hours after the inhalation of the last dose of the drug. This choice was based on the knowledge that tiotropium is the first long-acting bronchodilator, that provides the potential to reach a possible control of lung hyperinflation with a single daily dose, lasting at least 24 hours [13]. Significant reductions in parameters (RV, FRC, and IC) obtained with tiotropium are, in fact, found to still be present 24 hours after a single dose daily [14, 15]. The functional values recorded 24 hours after the last dose are definitely important, because the period before the next morning dose is not just the time in which it is expected the least effect of the drug, but also coincides with the time of day with greatest risk for lung hyperinflation [16]. It cannot also be excluded that the duration of the trial was too short. The parameters of lung hyperinflation with tiotropium seem, in fact, to increase over time, with further reductions observed after six weeks compared after three weeks in the same study [17].

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Table 1 – Basal characteristics of the studied population. Values are mean \pm SD.

Age	69.95 \pm 7.07
Sex (M/F)	14 M/7 F
Height (cm)	163.47 \pm 7.77
Weight (kg)	76.5 \pm 36.06
Smoking history (pack/yr)	46.77 \pm 21.21
FEV ₁ (% pred)	56.69 \pm 13.64
FVC (% pred)	80.07 \pm 16.75
FEV ₁ /FVC	56.15 \pm 11.20
IC (% pred)	76.38 \pm 21.76
FRC _{He} (% pred)	121.53 \pm 23.28
FRC _{pleth} (% pred)	147.69 \pm 23.82
RV _{He} /TLC%	133.35 \pm 14.87
RV _{pleth} /TLC%	143.00 \pm 18.04

Figure 1 – Changes in FEV₁, FVC, and IC induced by a 2-week treatment with tiotropium 18 µg/day. Values are mean ± SE and show changes recorded 24 hours after the last administration of tiotropium. ** p < 0.01 vs. baseline.

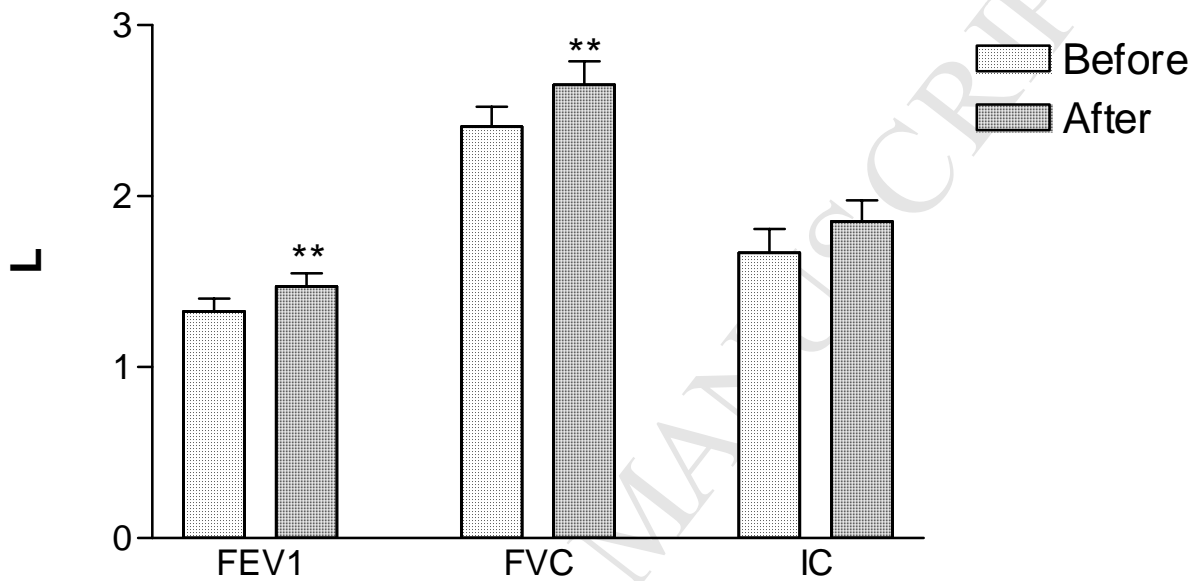


Figure 2 – Changes in FRC_{pleth} and FRC_{He} induced by a 2-week treatment with tiotropium 18 $\mu\text{g}/\text{day}$. Values are mean \pm SE and show changes recorded 24 hours after the last administration of tiotropium. *** $p < 0.001$ vs. baseline.

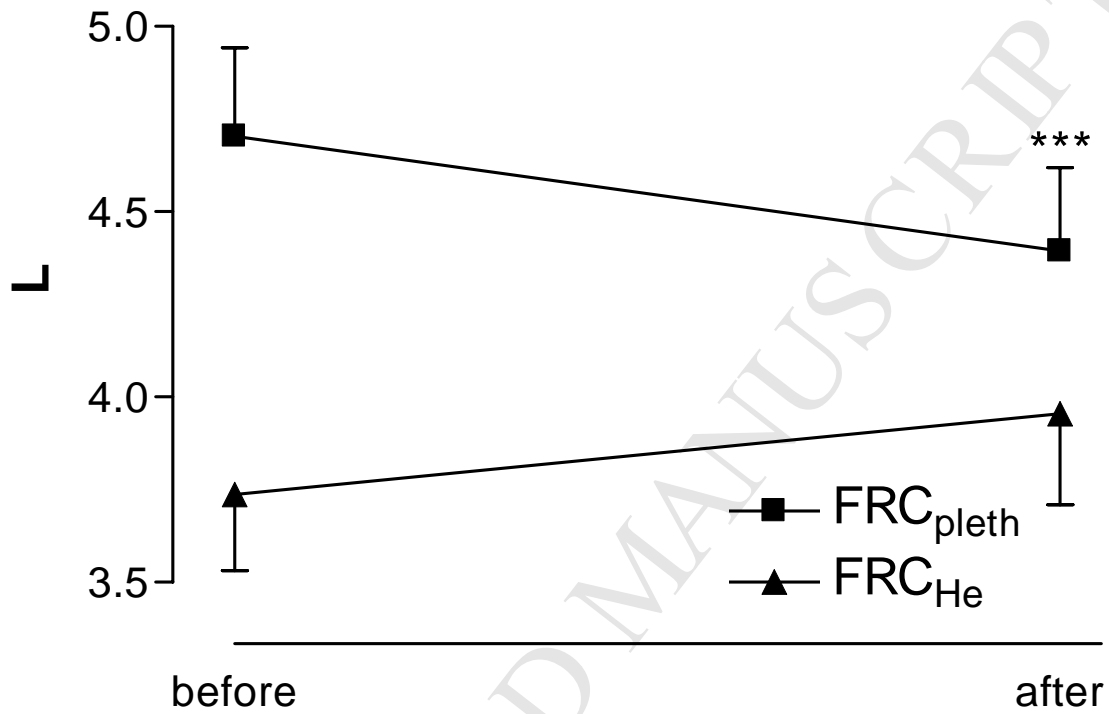


Figure 3 – Changes in RV_{pleth} and RV_{He} induced by a 2-week treatment with tiotropium 18 $\mu\text{g}/\text{day}$. Values are mean \pm SE and show changes recorded 24 hours after the last administration of tiotropium. ** $p < 0.01$ vs. baseline.

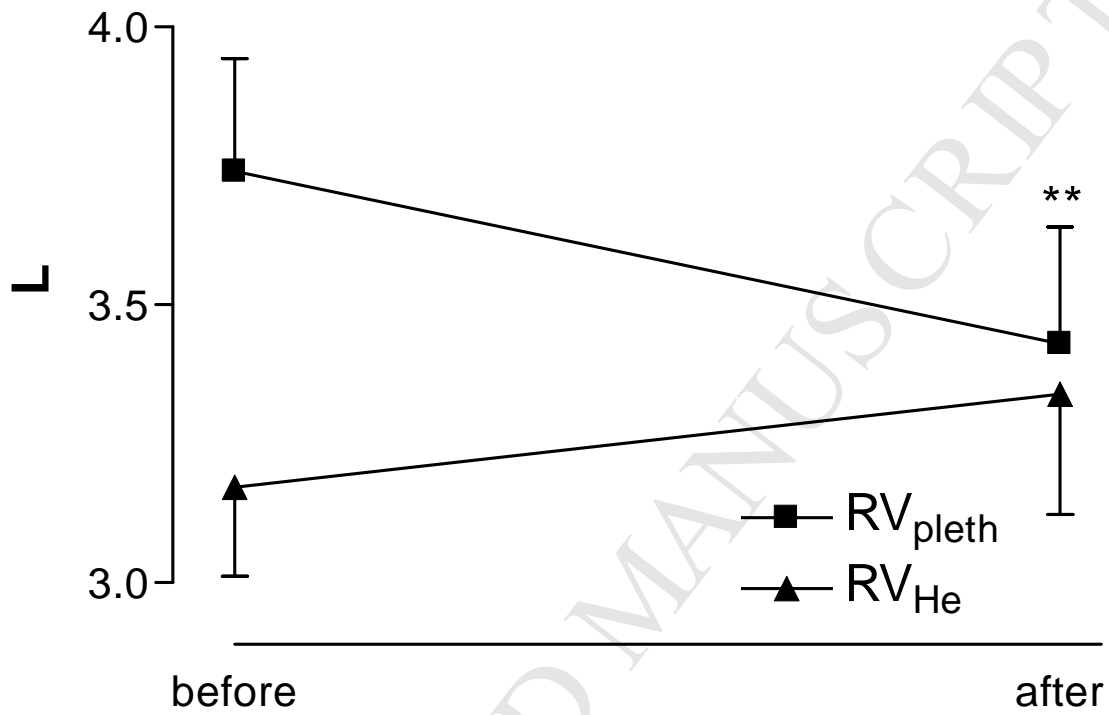


Figure 4 – Changes in TLC_{pleth} and TLC_{He} induced by a 2-week treatment with tiotropium 18 $\mu\text{g}/\text{day}$. Values are mean \pm SE and show changes recorded 24 hours after the last administration of tiotropium.

