Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
Bronconeumología

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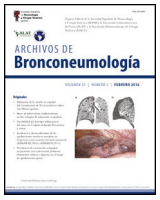

Scientific Letter

Integrating Spirometry With CT Scan as a Screening Tool in COPD Patients for Referral to Lung Volume Reduction Expert Centers

To the Director,

Severe COPD patients who remain highly symptomatic despite receiving optimal medical treatment could be potential candidates for lung volume reduction treatment (LVR).[1] To determine eligibility for LVR, body plethysmography is the preferred method for measuring static hyperinflation.[2] However, body plethysmography can be technically challenging and is not widely available in many countries worldwide. Other methods to measure static hyperinflation such as helium dilution fail in severe COPD patients.[3] Therefore, we aimed to investigate whether simplifying the assessment of hyperinflation by combining spirometry with inspiratory quantitative CT analysis (QCT) could be a useful screening tool when body plethysmography is not available to determine eligibility for lung volume reduction in COPD patients (oid), eliminating the need for body plethysmography in this part of the BLVR screening.[4]

This retrospective study used data from the Groningen severe COPD cohort (NCT04023409),[5] and included patients who visited our hospital between 2014 and 2019. The study was approved by the local ethics committee (METc2014/102). All patients signed informed consent. COPD patients with a post-bronchodilator FEV_1 >15% and <60% of predicted and RV <350% of predicted were included in this analysis if they performed both the spirometry, body plethysmography, and an inspiratory high-resolution CT scan on the same day.

All testing followed Guidelines of the European Respiratory Society (ERS)/American Thoracic Society (ATS). Global Lung Function Initiative (GLI) was used for reference equations. Spirometry was performed to obtain slow inspiratory vital capacity (VC) value. The unlinked method BP (Masterscreen PRO, Vyaire Medical) was used to measure intrathoracic gas volume (ITGV) and inspiratory capacity (IC). Total lung capacity (TLC) was calculated by the sum of ITGV_mean + IC_mean.

The inspiratory CT scan was performed under the guidance of a trained technician. Patients were instructed to breathe normally and then take a deep breath to achieve full lung inspiration, holding their breath at total lung capacity level for 2–3 s. All CT scans were conducted using a second-generation dual-source CT scanner (CT Somatom Definition Flash; Siemens, Erlangen, Germany). The scan utilized a pitch of 2.5, with a scanning duration of 1.5 s for a 40-cm thorax. The tube voltage was tailored to the patient's weight: 100 kVp for patients under 80 kg, 120 kVp for those weighing 80–110 kg, and 140 kVp for patients over 110 kg. The CareDose system was applied with a reference dose of 80 mAs.

Images were acquired with a collimation of 64 mm × 0.6 mm. For descriptive evaluation, reconstruction was performed using a hard kernel (B60f) with a reconstruction increment of 0.7 mm and a slice thickness of 1 mm. For quantitative analysis, a smooth kernel (B31f) was applied, with a reconstruction increment of 1.5 mm and a slice thickness of 1 mm. For QCT assessment (LungQ, Thirona, Nijmegen, The Netherlands), a smooth kernel (B31f) reconstruction of 1 mm slices was used. The total lung volume from the inspiration CT-scan represented the CT-derived TLC. The highest VC value obtained by spirometry (VC_spirometry) was used for calculation of RV_plethysmography and RV_CT-scan.

Paired *T*-tests were used to examine the difference in lung volumes between body plethysmography and CT-scan. Pearson correlations were used to explore the associations between lung volumes measured by body plethysmography and CT-scan. Bland–Altman plots were used to assess the proportional and systemic bias between body plethysmography and CT-scan. *P*-values <0.05 were considered statistically significant. Analysis was performed with Python (version 3.7.9) with the use of SciPy library (version 1.7.3).

Of the 1030 COPD patients in our cohort, a total of 808 patients (66% female, age 62 ± 7 years, FEV_1 29 ± 9% predicted, FVC 73 ± 17% predicted and FEV1/FVC ratio of 31 ± 7%) could be included after applying the in- and exclusion criteria. VC-spirometry was 3.00 ± 0.92 L. Both TLC_CT and thus the calculated RV_CT were 645 ± 429 mL ($P < 0.001$) lower compared to the body plethysmography values (Table 1). Pearson's correlation coefficient was $r = 0.96$ for absolute TLC and $r = 0.83$ for TLC% of the predicted value, and $r = 0.91$ for absolute RV, and $r = 0.87$ for RV% of predicted (all $P < 0.001$). Bland–Altman plots showed a systemic bias (Fig. 1A and C). The linear regression analysis, provided the following formula: *0.83 + 0.97*TLC_CT* which can be used to correct for the systemic bias between the two methods (Fig. 1B and D).

In this study, we investigated a simplified method to determine hyperinflation without the use of body plethysmography in COPD patients. By combining spirometry with inspiratory QCT we showed that this approach can be useful for LVR screening. Overall, the CT-scan method generated lower TLC values than the TLC measured with body plethysmography in most subjects, resulting in systematic lower RV values derived from CT.

The discrepancy between CT-derived and body plethysmography-derived TLC could be attributed to several factors. VC measured by spirometry and body plethysmography measurements are performed in seated position, while CT scan is performed in supine position. The difference in body position during measurements has been shown to influence volumes, with higher volumes typically observed in a seated position.[6] Also our previous work showed that CT-derived lung volumes are strongly associated with body plethysmography results in COPD.[7] Although there are statistically significant differences in TLC (lower for inspiration CT compared to plethysmography), these differences appeared to a systemic bias and can be adjusted for with the provided formula. However, the lack of standardized CT protocols and predefined criteria introduces variability, limiting the broader

https://doi.org/10.1016/j.arbres.2025.01.017

Please cite this article as: K. Klooster, J.T. Bakker, J.E. Hartman et al., Integrating Spirometry With CT Scan as a Screening Tool in COPD Patients for Referral to Lung Volume Reduction Expert Centers, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2025.01.017

Table 1
Lung Volume Results ($n = 808$).

	Body Plethysmography	CT Scan Derived	CT Scan Calculated
TLC, L	7.57 ± 1.46	6.92 ± 1.43	7.54 ± 1.39
% predicted	129.9 ± 13.4	118.5 ± 12.7	129.6 ± 12.8
RV, L	4.57 ± 1.03	3.92 ± 1.00	4.57 ± 0.97
% predicted	235.8 ± 45.8	203.0 ± 43.3	236.2 ± 44.3
RV/TLC ratio %	60.5 ± 8.2	57.7 ± 9.0	60.6 ± 8.2

Data are presented as mean ± standard deviation. Measurements were performed post-bronchodilator. Vital capacity (VC) measured during spirometry was used for calculation of residual volume. VC, spiro, was 3.00 ± 0.92 L. Lung volumes were measured using body plethysmography and derived from CT scan. Calculated volumes from CT scan were obtained by using the formula: 0.83 + 0.97*TLC CT-scan. RV: residual volume; TLC: total lung capacity.

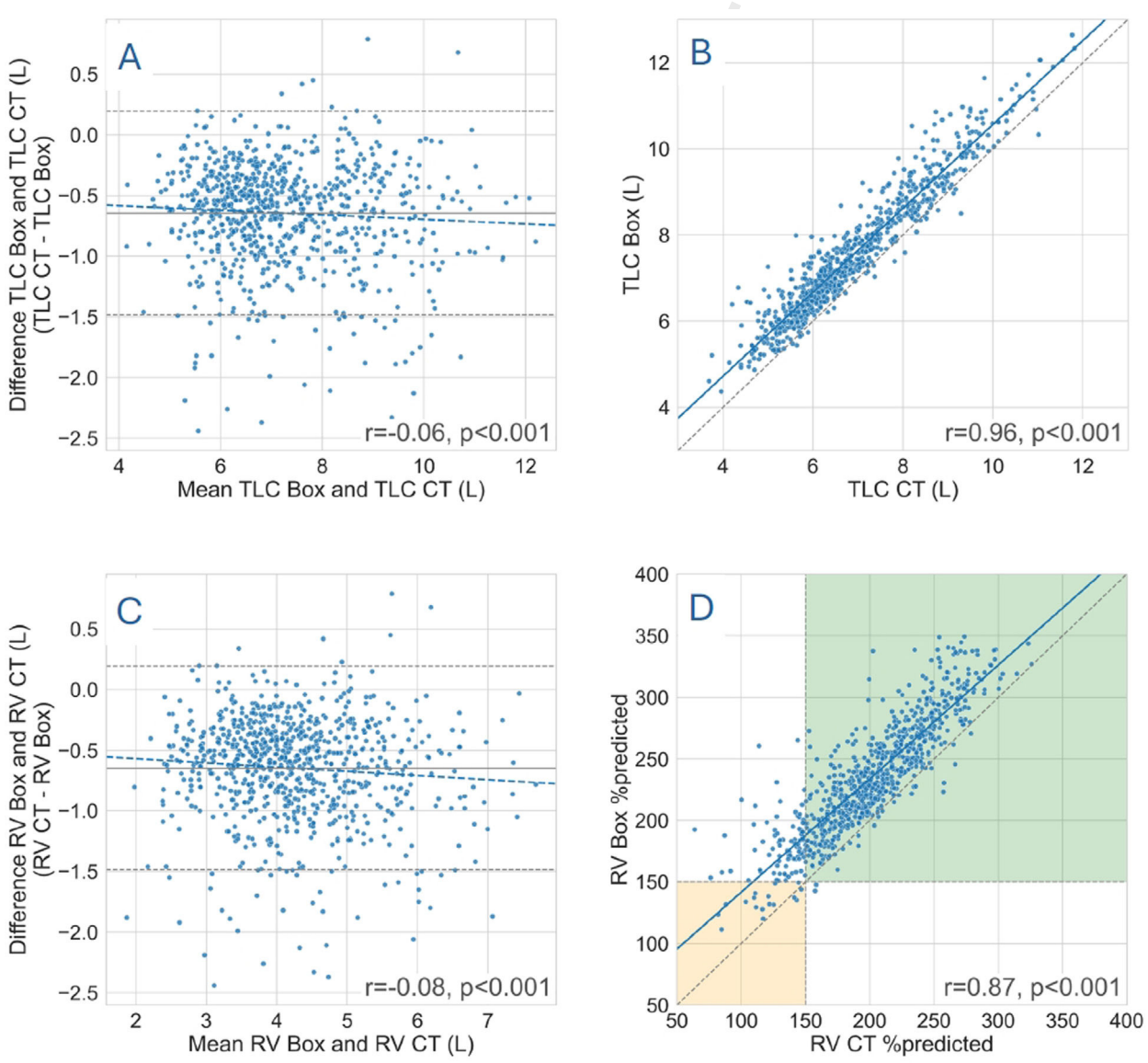

Fig. 1. Associations between CT-scan and BP-derived volumes ($n = 808$). (A and C) Bland–Altman plots comparing CT-scan and body plethysmography-derived measurements for (A) TLC derived from CT-scan, and (C) RV calculated from derived TLC from CT-scan (C). The continuous solid lines indicate the mean difference between CT and body plethysmography, the outer dashed lines indicate the 95% confidence intervals in the differences between CT-scan and body plethysmography, and the difference between these is the difference in limits of agreement. The dashed blue line in the middle of the figure indicates the linear regression signifying the proportional bias. (B and D) Scatter plots showing associations between CT-scan and plethysmography-derived volumes. (B) TLC derived from CT-scan with TLC obtained from plethysmography, and (D) RV % predicted value calculated from derived TLC from CT-scan (D). The green area indicates that both RV Box and the RV calculated from derived TLC from CT-scan are >150% of the predicted value. The yellow area indicates that both RV Box and the RV calculated from derived TLC from CT-scan are <150% of the predicted value. CT: computed tomography; TLC: total lung capacity, "Box" is an abbreviation of body plethysmography.

applicability of our regression model. Further validation in larger, diverse populations and across different clinical centers is necessary to confirm its accuracy and utility. Additionally, future studies could investigate other factors that might influence the regression model.

This study was conducted to investigate a simplified method to measure hyperinflation. This spirometry-QCT approach is intended as a screening tool to identify potential candidates for referral to LVR-expert centers. It does not replace comprehensive pulmonary function testing or clinical evaluation for determining final eligibility for LVR procedures. The role of this approach is to streamline patient selection and optimize resource allocation by identifying patients who may benefit from further LVR evaluation. Since a CT scan and QCT is always required for this assessment, it would be very convenient if all necessary information could be derived from it. Body plethysmography can be technically challenging to perform in severe COPD patients as it requires significant effort. Furthermore, the availability of body plethysmographs and trained staff to operate them is limited in many countries.

The current capabilities for QCT have lowered the barrier for evaluating a patient for LVR. Practically, when a patient with severe COPD is symptomatic despite optimal medical treatment, obtaining a CT scan is recommended.[1] By using the current advocated approach, an inspiration CT scan and a spirometry is all that will be needed to generate the necessary screening information regarding the degree of static hyperinflation, lobar volumes, the extent of emphysematous destruction of the individual lung lobes, and the fissure integrity.

To determine eligibility for LVR, a commonly used threshold for patient selection for LVR is RV $\geq$175% predicted. However, since there are substantial differences in predicted RV values between the GLI and European Community for Steel and Coal reference equations[9] this threshold has become less clear. Furthermore, patients with less hyperinflation (RV $\geq$150%) predicted can also benefit from BLVR.[8] Therefore, based on the results of spirometry-QCT approach, patients with a RV $\geq$150% could be candidates to be referred to an LVR-expert center.

One limitation of this study is the lack of standardized CT protocols across different clinical settings. Variability in factors such as breath-hold technique, scanner settings, and patient positioning may contribute to differences in lung volume measurements. Standardization of scan protocols specific to LVR screening is essential to ensure reproducibility and broader applicability of the results. Future research should aim to establish clear guidelines for CT acquisition to minimize variability and improve the reliability of the spirometry-QCT approach.

In conclusion, our findings demonstrate the potential that the integration of spirometry with inspiratory lung quantitative CT can serve as a simplified and effective screening tool to identify patients with severe COPD for referral to lung volume reduction expert centers. Given the systematically and significantly lower residual volume observed on spirometry-QCT approach when compared to body plethysmography, we recommend using a lower threshold of predicted RV percentage when applying the combined spirometry-QCT approach to consider patients to referral to LVR center using the following formula: 0.83 + 0.97*TLC_CT. Future research should prioritize the standardization of CT protocols. While promising, this screening tool is intended to complement, not replace, comprehensive pulmonary function testing in assessing suitability for LVR evaluation. With further refinement and validation, this approach has the potential to significantly enhance patient selection for LVR, improving access to treatment for patients worldwide.

CRediT Authorship Contribution Statement

KK: study design, data collection, data analysis, writing (original draft).

JB: data analysis, graphs design, writing (review and editing).

JEH: study design, data collection and writing (review and editing).

DJS: study design and writing (review and editing).

Funding

None declared.

Conflict of Interests

The authors state that they have no conflict of interests. Q2

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