The total-breath method yields higher values of DLCO and TLC than the conventional method

Rudolf A. Jörres[1*], Christian Buess[2], Andreas Piecyk[3], Bruce Thompson[4], Sanja Stanojevic[5] and Helgo Magnussen[6]

Abstract

Background The 2017 ATS/ERS technical standard for measuring the single-breath diffusing capacity (DLCO) proposed the "rapid-gas-analyzer" (RGA) or, equivalently, "total-breath" (TB) method for the determination of total lung capacity (TLC). In this study, we compared DLCO and TLC values estimated using the TB and conventional method, and how estimated TLC using these two methods compared to that determined by body plethysmography.

Method A total of 95 people with COPD (GOLD grades 1–4) and 23 healthy subjects were studied using the EasyOne Pro (ndd Medical Technologies, Switzerland) and Master Screen Body (Vyaire Medical, Höchberg, Germany).

Results On average the TB method resulted in higher values of DLCO (mean ± SD $\Delta = 0.469 \pm 0.267$; 95%CI: 0.420; 0.517 mmol*min-1*kPa-1) and TLC ($\Delta = 0.495 \pm 0.371$; 95%CI: 0.427; 0.562 L) compared with the conventional method. In healthy subjects the ratio between TB and conventional DLCO was close to one. TLC estimated using both methods was lower than that determined by plethysmography. The difference was smaller for the TB method ($\Delta = 1.064 \pm 0.740$; 95%CI: 0.929; 1.199 L) compared with the conventional method ($\Delta = 1.558 \pm 0.940$; 95%CI: 1.387; 1.739 L). TLC from body plethysmography could be estimated as a function of TB TLC and FEV_1 Z-Score with an accuracy (normalized root mean square difference) of 9.1%.

Conclusion The total-breath method yielded higher values of DLCO and TLC than the conventional analysis, especially in subjects with COPD. TLC from the total-breath method can also be used to estimate plethysmographic TLC with better accuracy than the conventional method.

The study is registered under clinicaltrial.gov NCT04531293.

Keywords Diffusing capacity, Lung volume measurements, Pulmonary function testing, Chronic obstructive pulmonary disease

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Results in short

The 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung proposed the "total-breath method" for the single-breath maneuver. We found that this method yielded higher values of DLCO and TLC than the conventional method.

Introduction

The single-breath diffusing capacity (DLCO) of the lung for carbon monoxide is a well-established functional measure with multiple clinical applications [1, 2]. In 2017, the ATS/ERS published recommendations for its measurement covering technical and methodological requirements. In addition to the conventional method, the technical standard described a procedure for the determination of alveolar volume (VA) in the assessment of diffusing capacity that was introduced in 1985 [3] and then [4] named the rapid gas analyzer (RGA) method, or alternatively [5] total-breath (TB) method. Instead of considering only an average value from a limited sample volume as in conventional sampling (CS), the total-breath method relies on measuring the entire course of exhaled tracer gas concentration, using a rapid gas analyzer (RGA). VA and the corresponding total lung capacity (TLC) are then derived from a mass-balance equation using the entire concentration curve (Fig. 1) [4]. As the total-breath method uses more of the available measured data, it offers the prospect to provide more accurate estimates of lung volume than the conventional method. Since the value of DLCO depends on that of VA, a change in method would also change DLCO values.

Since the values of TLC estimated via gas dilution are affected by inhomogeneity of ventilation, a key feature of COPD [6], the observed differences between the total-breath and the conventional method should become greater in people with more severe COPD. Moreover, the well-known difference between TLC measured via gas dilution and TLC measured via body plethysmography [7] might become smaller with the total-breath method, potentially improving the estimation of plethysmographic TLC from gas dilution.

We aimed to determine the impact of using the total-breath method in healthy subjects and those with COPD of different severities, by comparing DLCO and TLC estimated using the conventional and total-breath method. TLC values were also compared with those measured by body plethysmography.

Materials and methods

Recruitment of the study population

Consecutive patients with the clinical diagnosis of COPD [8] were recruited from the pulmonary department at the Hirslanden Hospital Zurich, Switzerland. Healthy subjects, who had no history of respiratory disease, were recruited from hospital staff. Subjects with other types of lung disease than COPD were excluded. The study protocol (clinicaltrial.gov NCT04531293, first trial registration 28/08/2020) was approved by the local ethics committee (Kantonale Ethikkommission Zürich (Cantonal Ethics Committee), BASEC 2020–02139), and all participants gave their written informed consent. All experiments

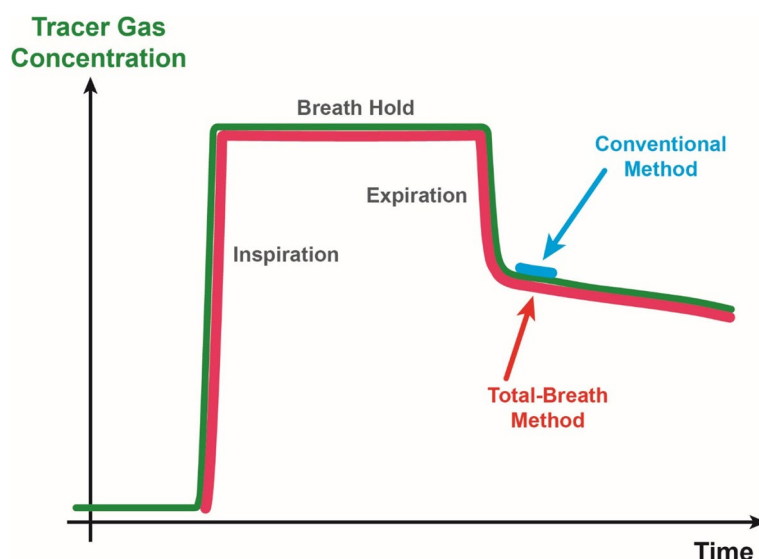**Fig. 1** Illustration of the two approaches regarding the total-breath method (TB) using a rapid gas analyzer (RGA) and the conventional sampling (CS) of the inert tracer gas during expiration in the single-breath assessment of CO diffusing capacity of the lung. Although the RGA provides a continuous signal over the whole course of expiration, in the CS method only a defined sample of 500 mL is used (see Materials and methods)

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were performed in accordance with relevant guidelines and regulations, in particular the Declaration of Helsinki.

Assessments

Spirometry was performed using the EasyOne Pro (ndd Medical Technologies, Switzerland) following international recommendations [9]. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and their ratio FEV_1/FVC were reported, with predicted values from GLI (Global Lung Function Initiative) [10]. Lung volume from body plethysmography (TLC_{body}) was estimated using the Master Screen Body (Vyaire Medical, Höchberg, Germany). Diffusing capacity for carbon monoxide (CO) was determined in a single-breath maneuver using the EasyOne Pro (ndd Medical Technologies, Switzerland) and the integrated rapid gas analyzer. The single-breath maneuver was performed twice, separated by at least 5 min [11], and expiration was terminated if a volume plateau was reached. Data was analyzed conventionally by averaging over a defined sample of expiratory volume (conventional sample of 500 mL, CS), or utilizing the total time course of in- and expiration (total-breath, TB) for helium concentration (see Fig. 1). The conventional analysis was available in the EasyOne Pro device (software version V3.7.2.2), which has been shown to yield reliable values in previous studies [12–15]. The total-breath analysis was performed via a custom algorithm after export of the raw data, using the entire tracer gas (helium) concentration during inspiration and expiration (see Fig. 1) within a mass-balance equation. DLCO and TLC were calculated using the residual concentration of helium in the exhaled air as measured at the start of each test. VA was related to TLC by dead space computed as 2.2 mL/kg body weight for $BMI < 30$ kg/m^2, and by $height^2$ (in m) divided by 189.4 for $BMI \geq 30$ kg/m^2 [4]. Predicted values were taken from the Global Lung Function Initiative reference equations [10, 16].

Statistical analysis

Continuous data were summarized as mean values and standard deviations (SD). Bland–Altman plots were used to assess the agreement between estimates of DLCO and TLC obtained by different methods. Pearson's correlation coefficients and linear regression analysis were employed to quantify associations between a set of explanatory variables (sex, age, height, BMI, Z-Scores of FEV_1 or FEV_1/FVC) and the differences between the values of TLC or DLCO determined by the two different methods, whereby FEV_1 or FEV_1/FVC were tested separately due to their collinearity. A similar approach was followed with plethysmographic TLC as dependent variable. Adjusted R^2 values and residual standard deviations (RSD) were

used to quantify the accuracy of predictions. Groups were compared using the unpaired t-test, or analysis of variance (ANOVA) with post-hoc comparisons according to Duncan in case of more than two independent groups. Outcome values estimated in the same subject were compared using the paired t-test.

The concordance between variables was quantified by their normalized root mean square difference (NSD), defined as standard deviation of the individual differences between two variables divided by their mean value [17]. This is a measure of the residual error of estimation of one variable from another variable after removing their potential systematic difference (bias). The sample size was based on findings by Horstman et al. [5]. Following the aim to detect a difference of the magnitude of 50% of its standard deviation in three pairwise comparisons at a total alpha of 0.05 and a power of 0.95, at least 69 subjects were needed; due to the probably higher variability particularly in patients with severe COPD we aimed at a final size of $n = 120$. Statistical significance was assumed for a type I error of $p < 0.05$. All statistical analyses were performed using the package SPSS (Version 26, IBM, Armonk, NY, USA).

Results

Study population

Data from 23 healthy subjects and 95 patients with COPD were available for analysis (Table 1). Subjects with airflow obstruction included all four GOLD grades; with more subjects with GOLD 1 and 2 compared to 3 and 4 (Table 1).

Agreement between the duplicate assessments

The time between the duplicate assessments was at minimum 312 s, with a median (quartiles) of 342 (330; 363) seconds. The repeatability of DLCO from the duplicate measurements was high for both the TB and CS method, mean values (95%CI) of differences between 1st and 2nd assessments being -0.002 (-0.069; 0.065) and -0.008 (-0.070; -0.055) mmol*min^{-1}*kPa^{-1}, respectively. Similar repeatability was observed for TLC, mean values (95%CI) of differences being -0.010 (-0.049; 0.029) and -0.018 (-0.050, 0.014) L for the TB and the CS method, respectively. Therefore, the mean values of the duplicate assessments were used in all subsequent analyses.

Lung diffusing capacity for CO

The correlation between the values of $DLCO_{TB}$ and $DLCO_{CS}$ was high ($r = 0.994$; $p < 0.001$). To elucidate their relationship in detail, Fig. 2A shows a Bland–Altman plot of the difference of $DLCO_{TB}$ and $DLCO_{CS}$ versus their mean value. On average ($\pm SD$), $DLCO_{TB}$ was

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Table 1 Characteristics of the patients

Variable	Group		
	Healthy	GOLD 1/2	GOLD 3/4
n	23	64	31
Age (y)	38.6 ± 12.4	71.9 ± 9.9	72.4 ± 6.8
Sex (m/f) (%)	61% / 39%	58% / 42%	45% / 55%
Height (m)	173.5 ± 11.7	171.1 ± 8.2	166.9 ± 8.7
BMI (kg/m^2)	23.1 ± 2.4	25.2 ± 4.2	25.4 ± 3.7
FEV_1 (L)	3.93 ± 0.87	1.82 ± 0.50	0.93 ± 0.24
FVC (L)	5.02 ± 1.09	3.30 ± 0.79	2.41 ± 0.58
FEV_1 (% predicted, GLI)	102.1 ± 7.4	66.7 ± 11.9	37.7 ± 8.5
FVC (% predicted, GLI)	106.8 ± 11.9	92.8 ± 16.1	74.9 ± 15.8
FEV_1 (Z-score, GLI)	0.180 ± 0.593	-1.929 ± 0.671	-3.495 ± 0.601
FVC (Z-score, GLI)	0.509 ± 0.823	-0.441 ± 0.966	-1.568 ± 1.035
FEV_1/FVC (Z-score, GLI)	-0.511 ± 0.817	-2.395 ± 0.988	-3.853 ± 0.705
$DLCO_{CS}$ (mmol*min^{-1}*kPa^{-1})	10.47 ± 3.02	5.60 ± 2.15	3.67 ± 1.73
$DLCO_{TB}$ (mmol*min^{-1}*kPa^{-1})	10.82 ± 3.03	6.06 ± 2.20	4.23 ± 1.80
VA_{CS} (L)	6.19 ± 1.20	5.26 ± 1.20	4.19 ± 0.82
VA_{TB} (L)	6.41 ± 1.21	5.75 ± 1.05	4.94 ± 1.11
TLC_{CS} (L)	6.34 ± 1.20	5.41 ± 0.97	4.34 ± 0.82
TLC_{TB} (L)	6.57 ± 1.24	5.89 ± 1.06	5.07 ± 1.14
TLC_{body} (L)	7.12 ± 1.30	6.84 ± 1.11	6.75 ± 1.55
$TLC_{body} - TLC_{CS}$ (L)	0.78 ± 0.20	1.43 ± 0.69	2.41 ± 1.08
$TLC_{body} - TLC_{TB}$ (L)	0.55 ± 0.22	0.95 ± 0.53	1.68 ± 0.95

COPD patients of GOLD grades 1–4 were pooled into two groups. Mean values ± SD are given. There were significant differences between groups in the distribution of men and women, as well as age, height and BMI ($p < 0.05$ each, ANOVA). Groups were also significantly different from each other ($p \leq 0.001$ each, ANOVA) in the parameters involving TLC and DLCO, with significant differences between all pairs of groups ($p < 0.05$, Duncan post hoc comparisons). Groups did not significantly differ in TLC_{body}

BMI body-mass index, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *DLCO* lung diffusing capacity for carbon monoxide, *VA* alveolar volume, *TLC* total lung capacity, *GLI* Global Lung Function Initiative. Subscripts: *TB* total-breath, *CS* conventional sample, *body* body plethysmography

higher by 0.469 ± 0.267 (95%CI: 0.420; 0.517; $p < 0.001$) mmol*min^{-1}*kPa^{-1} than $DLCO_{CS}$. The difference was systematically offset and not a function of the magnitude of DLCO, as it was not correlated with the mean value. The NSD between both values was 4.3%.

Accounting for sex, age, height and BMI as covariates, the difference between $DLCO_{TB}$ and $DLCO_{CS}$ increased as the FEV_1/FVC Z-Score decreased (adjusted $R^2 = 0.216$, Fig. 3A, $p < 0.001$). A similar result was observed for the ratio of $DLCO_{TB}$ to $DLCO_{CS}$ (adjusted $R^2 = 0.423$, Fig. 3B). Both associations were weaker in terms of adjusted R^2, when using the Z-Score of FEV_1, indicating the adequacy of FEV_1/FVC as associated index of airway obstruction.

Total lung capacity obtained via diffusing capacity manoeuvre

Over the whole range of values, the correlation between TLC_{TB} and TLC_{CS} was high ($r = 0.953$; $p < 0.001$). Figure 2B shows the results of Bland–Altman plots of the difference of TLC_{TB} and TLC_{CS} versus their mean value. Mean ($\pm$ SD) TLC_{TB} was higher by 0.495 ± 0.371 L than TLC_{CS} (95%CI: 0.427; 0.562 L; $p < 0.001$). Their difference did not significantly correlate with their mean value, and the NSD was 6.7%.

Using sex, age, height and BMI as covariates, again the Z-Score of FEV_1/FVC was found to be significantly associated with the difference between TLC_{TB} and TLC_{CS} ($p < 0.001$, adjusted R^2 0.417) or their ratio ($p < 0.001$, adjusted R^2 0.429) and being superior to the Z-Score of FEV_1.

Relationship of TLC from single-breath test to TLC from body plethysmography

Both TLC_{CS} and TLC_{TB} were correlated with TLC_{body} ($r = 0.709$ and 0.824, respectively; $p < 0.001$ each). The mean ($\pm$ SD) difference (95%CI) between TLC_{body} and TLC_{CS} was 1.558 ± 0.940 (95%CI: 1.387; 1.739) L and between TLC_{body} and TLC_{TB} 1.064 ± 0.740 (95%CI: 0.929; 1.199) L; for the differences in single groups see Table 1. The corresponding NSD values were 15.4% for TLC_{CS} and 11.7% for TLC_{TB}. Thus, TLC_{TB} was closer to TLC_{body} than TLC_{CS}.

We then elucidated the relationship between TLC values from gas dilution and plethysmography using regression analysis, assuming that their relationship depended on airway obstruction [18] choosing the Z-Scores of FEV_1 or FEV_1/FVC that should always be available in practice, in addition to sex, age, height, BMI as covariates. The dependent variables were the ratios or differences of TLC_{CS} and TLC_{TB} versus TLC_{body}. In terms of adjusted R^2, the Z-Score of FEV_1 turned out to be slightly superior to that of FEV_1/FVC for all of these outcomes. Figure 4A shows the ratios TLC_{CS}/TLC_{body} and TLC_{TB}/TLC_{body} plotted against the Z-Score of FEV_1, and Fig. 4B the respective differences.

Using linear regression analysis with TLC_{TB} as the only predictor, TLC_{body} could be estimated with a residual error of 0.720 L, which was reduced to 0.621 L by inclusion of the Z-Score of FEV_1 (adjusted R^2 0.676 and 0.756, respectively). Using TLC_{CS} as predictor, the residual errors were 0.895 and 0.745 L, respectively (adjusted R^2 0.499, 0.651). The NSD for the estimation of TLC_{body} from TLC_{TB} and FEV_1 Z-Score was 9.1%, for the estimation from TLC_{CS} and FEV_1 Z-Score 10.8%.

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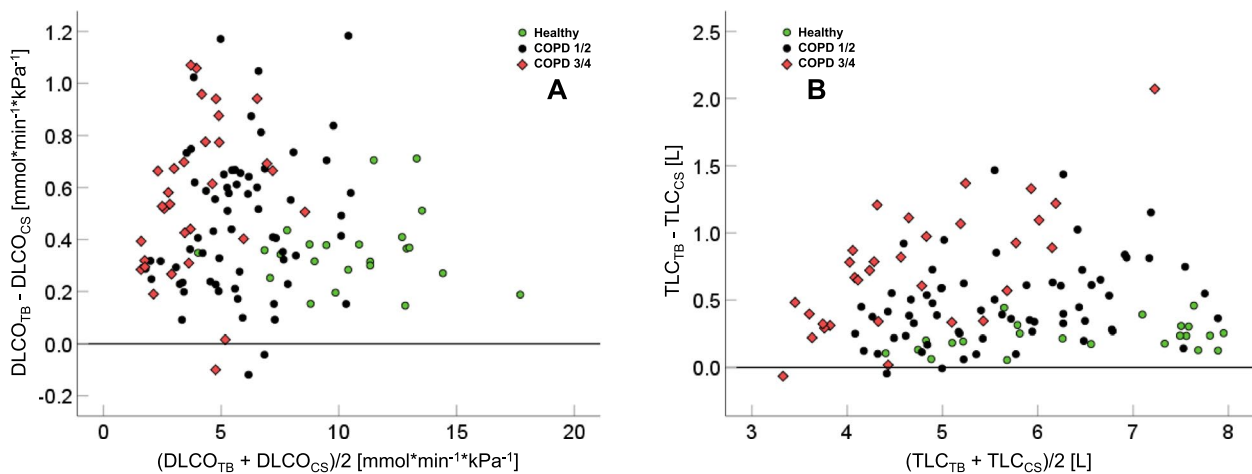
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Fig. 2 Bland–Altman plots of the difference between $DLCO_{TB}$ and $DLCO_{CS}$ (Panel **A**) or TLC_{TB} and TLC_{CS} (Panel **B**) versus their respective mean values. There was no statistical relationship between the difference and the mean. The lines indicate a difference of zero, and the three groups of healthy control subjects and patients of GOLD grades 1/2 or 3/4 are indicated by different symbols and colors
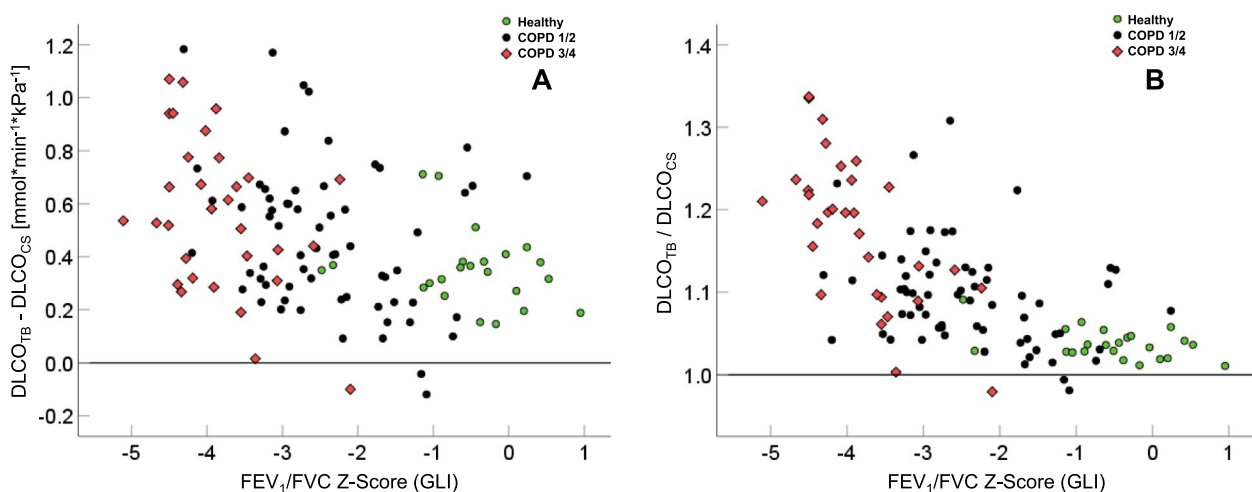

Fig. 3 Relationship of the difference between $DLCO_{TB}$ and $DLCO_{CS}$ (panel **A**) and their ratio (panel **B**) to the Z-Score of FEV_1/FVC. The horizontal lines indicate a ratio of one or a difference of zero, respectively, and the three groups of healthy control subjects and patients of GOLD grades 1/2 or 3/4 are indicated by different symbols and colors

Discussion

The recommended total-breath method for estimation of CO diffusing capacity (DLCO) and total lung capacity (TLC) resulted in higher values compared to the conventional analysis. The difference between estimates increased with the degree of spirometrically assessed airway obstruction in patients with COPD. Notably, total-breath TLC more closely agreed with TLC from body plethysmography; the latter could be estimated within less than 10% deviation, when taking into account the degree of airway obstruction.

In clinical practice, the single-breath manoeuvre is primarily performed to determine DLCO, while the assessment of VA, or equivalently TLC, is often secondary. The higher values of DLCO estimated using the TB method are relevant for at least two reasons. First, DLCO is a marker of parenchymal and/or pulmonary vascular dysfunction and airspace destruction, which typically occur in COPD and other lung diseases [1]. In contrast to computed tomography, DLCO has the advantage that it can be assessed repeatedly without radiation and is more affordable. However, in longitudinal analyses a change of method will require careful interpretation regarding comparability of values. Second, higher DLCO values using the TB method may require adaption of categorizations of clinical severity. As the ratio of $DLCO_{CS}$ to
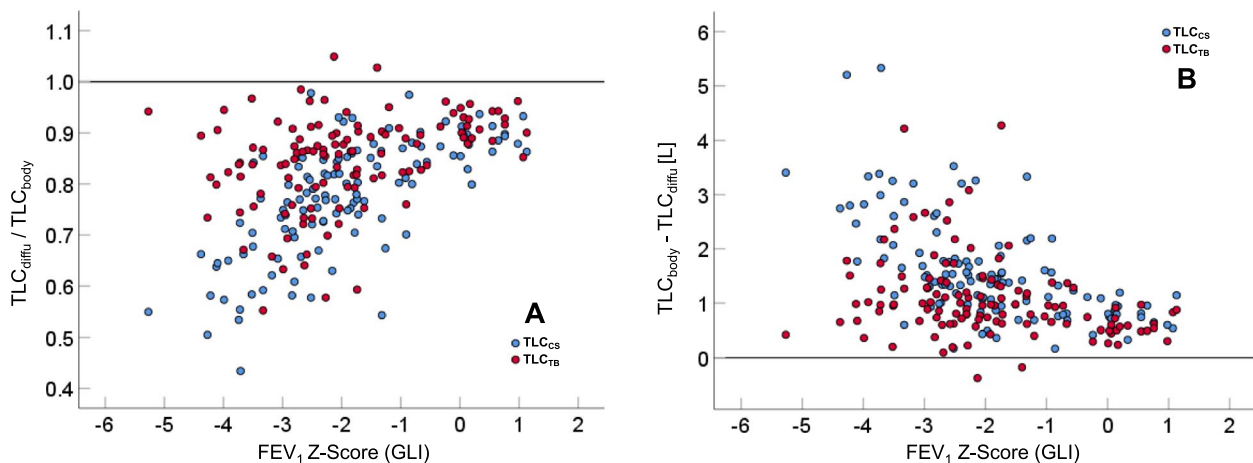
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Fig. 4 Association between the FEV_1 Z-Score, and either the ratio (panel **A**) or the difference (panel **B**) between TLC_{CS} determined by the conventional method and TLC_{TB} determined by the total-breath method, divided by TLC_{body} from body plethysmography. The two methods are indicated by different symbols (see insert) and collectively indicated by TLC_{diffu} on the vertical axes. The horizontal line indicates the value of one (panel **A**) or zero (panel **B**)

$DLCO_{TB}$ was close to one in healthy subjects (Fig. 3A, Table 1), mean predicted values may be kept but quantification of disease severity in COPD in terms of Z-Scores would be affected, if there should be differences in variance and consequently Z-Scores between the two methods; in contrast, grading in percent predicted might be less affected. In addition, further research is needed to reveal whether $DLCO_{TB}$ is superior to $DLCO_{CS}$ in showing better correlations with diagnostic features such as CT-based emphysema scores. No safety- or performance-related issues were observed with the TB method, as the changes solely referred to the mode of data evaluation.

Using the total-breath method, we found higher values for TLC, or equivalently VA, and DLCO. This raises the question to which extent the ratio of DLCO to VA, i.e. the transfer coefficient KCO, was affected. Its value, however, did not change, as the total-breath method altered VA and thereby DLCO by the same factor. The fact that KCO was not affected is relevant, as it is considered as valuable for the identification of causes underlying limitations of gas exchange capacity, in combination with DLCO [1, 2].

For the estimation of TLC via diffusion, the total volume was determined from helium dilution, taking into account the deadspace volume of the apparatus. In clinical practice, most often VA is chosen as volume parameter, requiring the assessment of anatomical deadspace. Moreover, the computation of DLCO involves VA and not TLC. Instead of a fixed deadspace volume of 150 mL, we used volumes computed from either body weight or height, depending on BMI, as previously recommended [4]. An additional analysis using a fixed value of 150 mL showed that, on average, the results regarding DLCO and VA were virtually unaffected by the choice of the

method (data not shown). For optimal estimation of dilution, we used the concentration of helium measured in the exhaled air at the start of each test and separated all duplicate assessments by more than 5 min, in line with recommendations [4]. The validity of assessments was underscored by the fact that the duplicate values showed only very small and non-significant differences.

Compared with TLC from body plethysmography, TLC_{TB} differed less than TLC obtained by the conventional method, especially in severe COPD (see Figs. 3 and 4). The difference between TB and plethysmographic TLC could be described as a function of the FEV_1 Z-Score. The NSD values compared favourably with those reported for different methods providing estimates of plethysmographic TLC [17], including helium and nitrogen washout, CT, and a newly proposed plethysmographic method [17] that showed an NSD of 8–9% compared to standard body plethysmography. Taking NSD as a measure, our observations suggest that the TB method provides more accurate estimates of TLC than the conventional approach, especially in COPD, and that the accuracy is sufficient for clinical purposes.

Regarding plethysmographic TLC, we identified FEV_1 as best parameter to describe the differences from TLC values obtained by the single-breath method. In a previous study [18], the method of multiple-breath helium dilution was used for comparison with VA assessed via single-breath dilution, and a computational method was described to derive estimates of multiple-breath TLC from single-breath VA. The difference between these values depended on airway obstruction quantified via the ratio FEV_1/FVC, thereby underlining that spirometric indices can account for the differences between TLC

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estimates from different procedures. It remains to be assessed whether the ability of TB analysis to provide better estimates also has the potential to improve clinical interpretation and diagnostic insight from functional data.

The difference between plethysmographic and diffusion-based TLC approached a constant offset in healthy subjects with high FEV_1 Z-scores (see Fig. 4B), which was in the range of 0.5 to 1.0 L. One might assume a homogeneous distribution of the tracer gas over the lungs in healthy subjects after deep inspiration, and thus only a small difference between plethysmographic and diffusion-based volumes, despite sampling errors [19]. As body plethysmographs are not subjected to the same strict requirements of comparability as commercial spirometers, the difference observed could also be due to a bias in the assessment of static lung volumes. For example, when comparing a plethysmograph of the brand that we used with that of another manufacturer, we previously found systematic differences of about 0.67 L in TLC in patients with COPD [20]. It is intriguing that in the study by O'Donnell and co-workers [21] body plethysmographic TLC appeared to be shifted upwards by about 0.5 to 1 L compared to CT-based values of TLC. Thus, potential differences between devices from different manufacturers have to be taken into account when comparing plethysmographic with diffusion-based TLC. As systematic differences between devices by different manufacturers might affect the interpretation of data in terms of predicted values, this topic seem worth of further examination.

Limitations

The number of patients of GOLD grades 3 and 4 was smaller than that of grades 1 and 2. A higher number of grade 3 and 4 patients might have allowed a more detailed investigation of the factors that explain the difference between plethysmographic TLC and TLC assessed by the TB method, as well as the difference between DLCO values determined by conventional and TB method. On the other hand, this question would probably have benefitted more from additional information such as CT scans in these patients, which were not possible in this study. Such information might be suitable to explain part of the differences between the methods compared in this work. In addition, two of the healthy control subjects showed a Z-Score of less than -1.645 for FEV_1/FVC. This was a percentage expected by chance, and we left these subjects in the group as we aimed to achieve a continuum of airway obstruction; their omission did not qualitatively change the results. We also considered the fact that the control group was much younger than the COPD group, as an advantage instead of a limitation, since we aimed

to include a group for the comparison of the methods, in which optimal lung ventilation and thus minimal differences between parameters could be assumed. From a clinical point of view, the inclusion of patients with restrictive lung disorders or with asthma would have been of interest. Although these patients probably would show similar results as the healthy control subjects, unexpected findings might occur that could be informative for phenotyping. We do not know, whether the TB method is available in other devices than that used in the present study; if that is the case, such devices should be compared to warrant a standard. Moreover, the use of methane instead of helium as tracer gas might result in lower values of TLC particularly in patients with severe COPD and therefore increase the discrepancy from plethysmographic TLC. In addition, it might be helpful to assess TLC_{body} using equipment from different manufacturers, as there is no obligatory standardization regarding these devices.

Conclusion

The total-breath method for computing TLC and DLCO from a single-breath manoeuvre, as recommended by the 2017 ATS/ERS DLCO technical standard, yielded higher values of DLCO than the conventional analysis, particularly in subjects with COPD. Moreover, TLC values were higher and closer to those from body plethysmography. These could be predicted with an accuracy of less than 10%, especially after inclusion of FEV_1 as additional variable. The observations suggest that the total-breath method yields more accurate values than the conventional method. Whether it additionally has the potential to improve clinical interpretation and provide novel diagnostic insight from functional data, remains to be studied.

Abbreviations

ATS	American Thoracic Society
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CS	Conventional sample
Δ	Delta
DLCO	Transfer factor for CO
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
KCO	Transfer coefficient for CO
NSD	Normalized root mean square difference
RGA	Rapid gas analyzer
SD	Standard deviation
TB	Total-breath
TLC	Total lung capacity
VA	Alveolar volume

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Declarations

Ethics approval and consent to participate
The study protocol (clinicaltrial.gov NCT04531293, first trial registration 28/08/2020) was approved by the local ethics committee (Kantonale Ethikkommission Zürich (Cantonal Ethics Committee Zurich), BASEC 2020–02139), and all participants gave their written informed consent. All experiments were performed in accordance with relevant guidelines and regulations, in particular the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
Research support: Christian Buess, employee of ndd reports financial support, administrative support, article publishing charges, and equipment, drugs, or supplies were provided by ndd Switzerland
Relationships: Christian Buess reports a relationship with ndd Switzerland that includes: employment.
Patents and Intellectual Property: There are not patents to disclose.
Other Activities: Helgo Magnussen received compensation for medical advice until 2022. Bruce Thompson and Sanja Stanojevic are members of the Advisory Board of ndd that has been created in 2023. Rudolf A. Jörres and Andreas Piecyk have nothing to disclose.

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