Application of Standard Diffusion Simulators in Quality Assessment of Pulmonary Diffusion Function Testing Instruments: A Postprint Study

Authors: Wu Zhongping, Huang Ruibo, Lin Kuiqing, Yu Xinxin, Zhong Liping, Chen Shubing, Zheng Jinping, Gao Yi, Gao Yi

Date: 2025-07-21T00:00:00+00:00

Abstract

Background The accuracy of lung diffusion function instruments directly affects clinical diagnosis and treatment decisions for pulmonary diseases; however, performance drift and measurement errors occur after long-term use of the instruments. Currently, clinical practice mostly employs daily calibration syringe calibration and biological human verification, yet their insufficient sensitivity makes it difficult to detect potential errors in the instruments. Therefore, there is an urgent need to explore more accurate and objective methods for instrument quality assessment.

Objective To use a standard diffusion function simulator to simulate human subjects for single-breath diffusing capacity testing of lung diffusion function, assess the accuracy of lung diffusion function instruments, correct the causes of instrument errors based on test results, observe the post-correction results and their duration of maintenance, and then discuss the application value of this method in combination with biological human verification.

Methods A standard diffusion function simulator (Hans Rudolph series 5560, U.S.A) was used with three carbon monoxide concentrations (0.08%, 0.10%, 0.13%) in gas mixtures and three inspired volumes (1.5 L, 3 L, 4.5 L) combined respectively to simulate subjects for single-breath diffusing capacity testing. The accuracy of four lung diffusion function instruments (two brands with two models each) was assessed as baseline using an acceptable range of absolute error <2 mL · min-1 · mmHg-1 between measured and target values of diffusing capacity of the lung for carbon monoxide (DLCO), while analyzing sources of instrument error. Corresponding corrections were then made based on the errors, and changes in instrument accuracy before and after correction and within 3 months

were compared. Simultaneously, combined with biological human verification, measurement differences between different instruments were observed.

Results At baseline, 50% (2/4) of instruments had a mean absolute error of DLCO >2 mL · min-1 · mmHg-1. Error sources varied among instruments, possibly due to damaged instrument accessories, incorrect operation methods, calibration syringe leakage, and other causes. After making corresponding corrections to the errors, all instruments achieved a mean absolute error of DLCO <2 mL · min-1 · mmHg-1 (P<0.001), which could be maintained for 3 months. After correction, differences in biological human measurements between different instruments decreased, particularly for DLCO measurement range and coefficient of variation (CV), where the differences were statistically significant (P<0.05).

Conclusion The accuracy of lung diffusion function testing instruments used clinically for long periods varies significantly, with large measurement differences between different instruments. The method of using a simulator for quality assessment of lung diffusion function testing instruments is effective and feasible, capable of assessing instrument accuracy and compensating for the limitations of daily calibration. Regular use of simulators for quality assessment and quality control is recommended.

Full Text

Application of Standard Diffusion Simulators in Quality Assessment of Pulmonary Diffusion Function Testing Instruments

WU Zhongping, HUANG Ruibo, LIN Kuiqing, YU Xinxin, ZHONG Liping, CHEN Shubing, ZHENG Jinping, GAO Yi*

The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China

Corresponding author: GAO Yi, Professor; E-mail: misstall2@163.com

Abstract

Background: The accuracy of diffusion capacity of the lung for carbon monoxide (DLCO) testing directly influences clinical decision-making in the diagnosis and treatment of pulmonary diseases. However, long-term instrument use leads to performance drift and measurement errors. Currently, daily calibration syringe checks and biological human verification are commonly used in clinical practice, but their sensitivity is insufficient to detect potential instrument errors. Therefore, more accurate and objective methods for instrument quality assessment are urgently needed.

Objective: To simulate single-breath DLCO testing using a standard diffusion simulator to evaluate the accuracy of DLCO instruments, correct identified errors, observe post-calibration outcomes and maintenance duration, and explore

the application value of this method in combination with biological human verification.

Methods: A standard DLCO simulator (Hans Rudolph series 5560, USA) was used to simulate single-breath DLCO testing with three carbon monoxide concentrations (0.08%, 0.10%, and 0.13%) and three inhalation volumes (1.5 L, 3 L, and 4.5 L). An absolute error between measured and target DLCO values of less than 2 $mL \cdot min^{-1} \cdot mmHg^{-1}$ was considered acceptable. The accuracy of four DLCO instruments (two brands, each with two models) was assessed as baseline, and error sources were analyzed. Instruments were then calibrated according to identified errors, and accuracy changes were compared before and after calibration and within three months post-calibration. Biological human verification was used to observe measurement differences between instruments.

Results: At baseline, 50% (2/4) of instruments exhibited average absolute DLCO errors exceeding 2 $mL \cdot min^{-1} \cdot mmHg^{-1}$. Error sources varied by instrument and included damaged accessories, operational errors, and calibration syringe leaks. After calibration, all instruments achieved average absolute DLCO errors below 2 $mL \cdot min^{-1} \cdot mmHg^{-1}$ ($P<0.001$), which was maintained for three months. Post-calibration differences in biological human measurements between instruments decreased significantly, particularly in the extreme difference and coefficient of variation (CV) of DLCO measurements ($P<0.05$).

Conclusion: The accuracy of clinically used DLCO instruments varies considerably after long-term use, with large inter-instrument measurement differences. Using standard simulators for quality assessment is effective and feasible, enabling accuracy evaluation and compensating for limitations of daily calibration. Regular simulator-based quality assessment and control are recommended.

Keywords: Pulmonary diffusing capacity; Pulmonary diffusion function instrument; Accuracy; Simulator; Diffusion capacity of the lung for carbon monoxide

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Pulmonary diffusion function is a crucial indicator for assessing gas exchange efficiency at the alveolar-capillary membrane. It aids in diagnosing, quantitatively evaluating, and monitoring pulmonary diseases affecting gas exchange, such as emphysema and pulmonary fibrosis, and is widely used for preoperative risk assessment, postoperative change detection, drug efficacy evaluation, and occupational lung disease assessment. The single-breath method is the primary approach for measuring pulmonary diffusion function, with DLCO being the most important parameter. DLCO instruments primarily consist of gas analyzers and spirometers. With increased usage and age, measurement accuracy for both gas and volume may drift, and instrument wear can affect accuracy. Furthermore, different instrument types employ varying measurement methods and principles, potentially causing substantial differences in diffusion measurements between and even within laboratories. The accuracy and variability of diffusion measurements have long concerned pulmonary function laboratories worldwide,

necessitating standardized simulators to calibrate and verify instrument reliability.

The 2017 American Thoracic Society (ATS)/European Respiratory Society (ERS) joint guidelines for diffusion capacity testing recommend using diffusion simulators for linearity testing of diffusion gases. Several scholars have reported that standard simulators can identify measurement deficiencies, but these studies did not specifically explore contributing factors or whether reducing instrument errors can decrease inter-instrument measurement differences. Therefore, this study employed a standard diffusion simulator to assess DLCO instrument accuracy, investigate error factors, and evaluate whether correction could reduce inter-instrument differences, combined with biological human testing to explore the simulator' s application value.

1.1 Study Subjects

From March to July 2021, four DLCO instruments were tested at the Pulmonary Function Laboratory of the National Clinical Research Center for Respiratory Disease in Guangzhou, China. Instruments were coded by brand and model: Instrument A (Cosmed Quark PFT4, 10 years of use), Instrument B (Cosmed Quark Ergo, 1.5 years), Instrument C (Jaeger Masterscreen-PFT, 9.5 years), and Instrument D (Jaeger Masterscreen-Bodybox, 4 years). All instruments except C used rapid gas analyzers (RGA); Instrument C used a classical gas analyzer. All bore CE marks and underwent regular maintenance per manufacturer instructions, including daily gas analyzer self-checks and spirometer volume calibration before each workday.

The simulator used was a Hans Rudolph series 5560 (USA), featuring two high-precision cylinders (5.5 L and 2.5 L, $±$15 mL error) to simulate breathing and three gas bottle baskets holding simulated gas mixtures. EasyLab QC software calculated target simulator values [Figure 1: see original paper].

Two healthy, non-smoking pulmonary function technicians (one male, one female) served as biological control subjects . The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (approval number: 2020124).

1.2 Methods

1.2.1 Pre-test Preparation 1.2.1.1 Simulator preparation: Three precision gas mixtures with different known CO concentrations and tracer gases were prepared to simulate exhaled breath. Depending on instrument brand requirements, either helium (He) or methane (CH_4) served as tracer gases, yielding six gas cylinders (Deli Messer, Guangzhou Foshan) with $±$1% precision. Considering typical Chinese population lung function characteristics, three CO concentrations were combined with three known inhalation volumes (VI) to create nine gas/VI combinations , with each combination simulating one subject.

1.2.1.2 Instrument preparation: Before simulator testing, all four instruments underwent environmental calibration, volume calibration, gas calibration, and calibration syringe DLCO checks, with results recorded. The calibration syringe DLCO check involved connecting a standard 3-L syringe to the instrument in normal test mode, simulating 4-5 tidal breaths, completely emptying the syringe during deep exhalation, opening the instrument valve before deep inspiration to fully inhale test gas into the syringe, waiting 10 seconds, then completely exhaling syringe contents into the instrument mouthpiece for DLCO calculation. The acceptance criterion was DLCO <0.166 mmol $\cdot$ min^{-1} $\cdot$ kPa^{-1} or <0.5 mL $\cdot$ min^{-1} $\cdot$ mmHg^{-1}.

1.2.2 Biological Human Testing After instrument calibration, biological human testing was performed. Each instrument underwent at least two DLCO tests with $ $4-minute intervals, achieving quality grade B or higher per 2017 ATS/ERS guidelines. Mean DLCO values were recorded. To avoid test interference from multiple same-day measurements, each instrument was tested weekly on separate days (17:00-19:00). Inter-instrument differences were assessed using extreme differences (maximum minus minimum) and coefficient of variation.

1.2.3 Simulator Testing Simulator testing mimicked subject DLCO testing procedures. For each gas/VI combination (e.g., LL combination in), the simulator' s three-way valve connected the large cylinder to the outlet and the small cylinder to the low-CO gas bottle, which was filled completely (residual gas was purged when changing concentrations). The large cylinder' s plunger was set to 1.5 L, then connected to the instrument sensor. The plunger simulated 4-5 tidal breaths; after stable baseline, complete exhalation to residual volume was performed while opening the instrument valve, followed by rapid, uniform inspiration to total lung capacity within 2 seconds. After a (10$±$2)-second breath-hold, the three-way valve was manually switched to connect the small cylinder, whose contents were completely "exhaled" into the instrument. The instrument calculated DLCO [10,17]. After 4-5 minutes for gas line purge and zero stabilization, each combination was repeated twice, yielding 18 DLCO values per instrument. All procedures followed ATS/ERS standards and manufacturer specifications, performed by the same technician.

Measured breath-holding time (BHT), inspired CO concentration (FICO), and inspired tracer gas concentration (FITR) were entered into EasyLab QC software to calculate target DLCO values using Formula 1 [10,12]. VI, exhaled CO concentration (FECO), and exhaled tracer gas concentration (FETR) used known target values. Absolute error and percentage error were calculated using Formulas 2 and 3.

Formula 1: DLCO = CorrVI/(PB-47) $\times$ (STPD factor) $\times$ (FICO$\times$FETR)/(FECO$\times$FITR)
Note: CorrVI = inhaled volume minus dead space; PB-47 = atmospheric pressure minus saturated water vapor pressure; t = breath-holding time; STPD factor = conversion factor to standard temperature and dry pressure conditions.

Formula 2: Absolute error = |Instrument measured value - Simulator target value|

Formula 3: Absolute error percentage = (Instrument measured value - Simulator target value) / Simulator target value

1.2.4 Instrument Evaluation 1.2.4.1 DLCO acceptability criterion: Average absolute DLCO error <2 $mL \cdot min^{-1} \cdot mmHg^{-1}$ indicated good accuracy [10,18].

1.2.4.2 Error assessment: Per Formula 1, accuracy of VI, FECO, and FETR affects DLCO accuracy. Error analysis was performed based on individual metric deviations. Acceptable error standards [11-12] were: VI percentage within 3%; FECO within 0.005%; FETR within 0.005% for CH_4 or 0.17% for He.

1.2.5 Instrument Calibration Baseline simulator testing identified errors in VI, FECO, and FETR. Corresponding corrective measures were implemented: VI errors from calibration syringe leaks, volume calibration issues, or mouthpiece leaks; gas measurement errors from sampling line blockages, analyzer inaccuracies, or operational errors. Corrections included replacing calibration syringes, accessories, or modifying procedures. Monthly simulator tests were performed for three months to monitor accuracy changes. Pre- and post-calibration absolute errors and biological human test results were compared.

2.1 Simulator Testing Results

Pre-maintenance average absolute DLCO accuracies for the four instruments were $(5.539\$\pm4.134), (2.968\pm3.402), (1.076\pm0.565), and (1.549\pm0.983) mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}\$$, with only 50% (2/4) within acceptable range [Figure 3: see original paper]. Error sources varied, including equipment factors and operational issues . Volume measurement (VI) errors stemmed from calibration syringe leaks causing inaccurate volume calibration, damaged accessories, and incorrect calibration procedures (particularly for Instruments A and B). Gas measurement (FECO, FETR) errors primarily resulted from sampling line issues, though in Instrument A, 管路零件损坏 caused leaks affecting gas accuracy, and in Instrument C, premature DLCO calculation before automatic display increased gas concentration measurement differences—issues undetectable through self-calibration.

After calibration, VI and FECO measurements improved significantly ($P<0.05$) [FIGURE:4-5], while FETR errors showed no significant reduction [Figure 6: see original paper], though their impact on DLCO accuracy was minimal. All instruments achieved acceptable post-calibration DLCO average absolute errors, with significant improvements in Instruments A, B, and C ($P<0.01$) that were maintained for three months [Figure 3: see original paper].

2.2 Inter-Instrument Biological Human Verification

Biological control testing differences are shown in and [FIGURE:7-8]. At baseline, BC1 mean DLCO values across instruments were $(42.635\$\pm0.205), (34.160\pm0.905), (29.370\pm0.212), and (34.690\pm5.190) mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}, showing significant differences (P = 0.032) with extreme differences of 12.97-13.56 mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}\$$ and CV >10% (maximum 15.29%). Post-calibration, mean DLCO values were $(30.638\$\pm1.385), (30.738\pm2.068), (30.046\pm0.994), and (31.942\pm1.512) mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}, with no significant differences (P = 0.062), extreme differences reduced to 1.58-5.43 mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}\$$, and CV ranging 1.98%-7.21%.

For BC2, baseline mean DLCO values were $(27.320\$\pm1.047), (21.410\pm0.636), (20.065\pm0.332), and (21.140\pm0.001 min^{\{-1\}\cdot mmHg}\{-1\}, showing significant differences (P = 0.001) with extreme differences of 7.75-6.75 mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}\$$ and CV >10% (maximum 13.40%). Post-calibration, values were $(19.085\$\pm0.919), (18.693\pm0.701), (19.772\pm0.654), and (19.512\pm0.842) mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}, still differing (P = 0.021) but with reduced extreme differences (1.13-2.85 mL \cdot min^{\{-1\}\cdot mmHg}\{-1\}\$$) and CV (2.22%-5.77%).

Instruments A and B showed significant differences in both BC1 and BC2 before and after calibration (P<0.05). Instrument D showed significant differences only for BC2 (P<0.001). Instrument C showed no significant differences for either control, with the smallest standard deviation and highest stability post-calibration [FIGURE:7-8].

Discussion

The accuracy and variability of DLCO instruments have long troubled pulmonary function laboratories. Clausen et al. found inter-laboratory CV for biological controls could reach 12.7%, with intra-laboratory DLCO test CV higher than forced vital capacity, making biological human verification alone insufficient for accurate performance assessment.

Despite pre-test environmental calibration, volume verification, gas calibration, and calibration syringe DLCO checks per guidelines, simulator testing revealed substantial accuracy differences among the four instruments in the same laboratory, with average absolute DLCO errors exceeding 5 $mL \cdot min^{-1} \cdot mmHg^{-1}$ and inconsistent accuracy across VI, FECO, and FETR metrics. Only 50% of instruments met acceptable DLCO measurement ranges. Biological human testing also revealed significant inter-instrument DLCO differences, with CV exceeding 10% (maximum 15.29%), confirming that daily calibration alone cannot ensure accuracy.

Error sources included both equipment wear and non-equipment factors. Calibration syringe leaks significantly impacted volume measurement accuracy. While guidelines require regular syringe quality checks, most Chinese pulmonary function laboratories lack dedicated equipment and spare syringes for this purpose. Future calibration promotion efforts must emphasize syringe quality control importance. Incorrect calibration procedures also caused errors; removing

Instruments A and B' s sensors from stands during calibration affected volume accuracy. Though manufacturer instructions indicated stand removal shouldn' t affect accuracy, recalibrating with sensors on stands significantly reduced volume measurement errors. In Instrument C, premature DLCO calculation before automatic display increased gas concentration measurement differences. Thus, standard simulators can identify both instrument deficiencies and operator errors, particularly valuable in laboratories with frequent staff turnover where standardized procedures reduce measurement errors.

Calibration based on identified errors improved DLCO measurement accuracy and reduced inter-instrument differences in biological human testing. Inter-instrument CV decreased from 11.84%-15.29% to 1.98%-7.21%, with 80% (16/20) of tests stabilizing below 5%. These results confirm the simulator method' s value in identifying instrument and operational issues, improving accuracy through targeted correction, and reducing inter-instrument variability. Simulator use should not be overlooked when developing more accurate DLCO reference equations or conducting multi-center longitudinal studies.

This study defined acceptable DLCO deviation as $ $2.0mL \cdot min^{\{-1\} \cdot mmHg}\{-1\}, referencingstudiesbyPunjabietal., Hegewaldetal., andGochicoa - Rangeletal., thoughJensenetal.used3mL \cdot min^{\{-1\} \cdot mmHg}\{-1\}$. Specific thresholds should consider study design and should not serve as performance standards for new instruments, which may require stricter criteria.

This study used simulator testing to identify error sources and defined acceptable ranges for VI, FECO, and FETR based on 2017 guidelines. VI absolute accuracy percentage was defined as instrument error (2.5%) plus syringe error (0.5%). FECO and FETR absolute accuracy ranges were defined as maximum instrument error (0.003%) plus gas error (~0.002%). Post-maintenance, VI and FECO errors fell within acceptable ranges. Although FETR errors couldn' t be further reduced due to lack of replaceable equipment, this limitation didn' t significantly impact DLCO accuracy assessment. Different instrument types employ varying DLCO measurement and calculation methods; for example, RGA systems differ from classical systems in VA determination, affecting target DLCO calculations. Therefore, corresponding calculation methods must be used based on instrument principles. Current simulator software calculations are better suited for classical than RGA systems, representing a simulator limitation. However, simulators can still assess VI, FECO, and FETR accuracy to improve DLCO measurement, as this study has validated. Future research should explore simulators specifically for RGA systems.

In conclusion, clinically used DLCO instruments show considerable accuracy differences and inter-instrument variability. Simulator-based quality assessment is effective and feasible, evaluating instrument accuracy while compensating for daily calibration limitations. Regular simulator-based quality assessment and control are recommended.

Funding: National Science and Technology Major Project for Prevention and

Treatment of Cancer, Cardiovascular and Cerebrovascular Diseases, Respiratory and Metabolic Diseases (2023ZD0506300)

Conflict of interest: None declared.

Author contributions: WU Zhongping, HUANG Ruibo, and LIN Kuiqing contributed to study design, data collection, statistical analysis, and manuscript writing. ZHENG Jinping, YU Xinxin, ZHONG Liping, and CHEN Shubing contributed to study implementation, evaluation, and revision. GAO Yi contributed to quality control and revision.

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Received: January 13, 2025; Revised: March 16, 2025
Edited by JIA Mengmeng

Note: Figure translations are in progress. See original paper for figures.