

D_{LCO} Biologic Quality-Control Findings From a Multi-Center Global Study

Ellen A Becker, Ellen M Moran, Jason B Blonshine, and Susan B Blonshine

BACKGROUND: The 2017 American Thoracic Society/European Respiratory Society (ATS/ERS) diffusing capacity of the lung for carbon monoxide (D_{LCO}) standards specify a control rule for assessing biologic quality control (BioQC) but have limited guidance on how to establish expected values for control rule variables. This study aimed to determine expected values for D_{LCO} BioQC using coefficient of variation (CV) and compare that the mean \pm 2 SD control rule yields the same precision as mean \pm 12% of the mean. **METHODS:** D_{LCO} BioQC data were collected from a multi-center inhaled medication study. This descriptive study spanned 42 months ending in 2018. The annual D_{LCO} CV was based upon 10 D_{LCO} values separated by at least 5 d. The root mean square CV (RMSCV) was computed for each year and Friedman test evaluated within subject annual CV changes. Ninetieth percentile values were computed for annual control rule limits/mean D_{LCO}. **RESULTS:** Of 217 BioQCs, the study's first year had 168 subjects with fewer in subsequent years. Annual CV values from RMSCV were 5.3, 4.5, and 4.6% in years 1, 2, and 3, respectively. No change was seen in the CV for those subjects with data for all 3 years, $n = 24$, $P = .07$. The 90th percentile of measurements 2 SD/mean D_{LCO} were 15, 12.4, and 11% in years 1, 2, and 3, respectively. **CONCLUSIONS:** A D_{LCO} BioQC CV \leq 6% is achievable across multiple sites, technologists, and brands of equipment. This CV value assures that measurements for control rule variables emerge from an expected range. A control rule of mean \pm 2 SD appeared to yield similar results as the mean \pm 12% of the mean rule reported in the 2017 ATS/ERS D_{LCO} standards. *Key words:* D_{LCO}; coefficient of variation; quality control; biologic control; control rule. [Respir Care 2023;68(9):1245–1253. © 2023 Daedalus Enterprises]

Introduction

The diffusing capacity of the lung for carbon monoxide (D_{LCO}) in a single-breath-hold maneuver measures the lung's ability to transfer gas molecules from alveolar space into pulmonary vasculature.¹ D_{LCO} is routinely measured in pulmonary function testing and is a noninvasive surrogate of oxygen uptake in the lung. However, calibration and quality control (QC) are vital to ensure the accuracy and precision of D_{LCO} measurements.^{1,2} Equipment and performance errors may affect medical decisions, resulting in harm to patients through incorrect or delayed treatment.³ Thus, clinical pulmonary function laboratories (PFLs) require strong QC programs to assure their systems perform as expected.

Four components of planning a QC strategy include (1) selecting appropriate control materials (subjects in the case of a biologic QC [BioQC]), (2) determining expected values for control materials, (3) timing of control measurements, and (4) control rules to identify out-of-control situations.³

The 2017 American Thoracic Society/European Respiratory Society (ATS/ERS) D_{LCO} standards recommend conducting BioQC on a weekly basis to assess equipment variation, technologist performance, and variations in human physiology. PFLs recruit healthy biologic control subjects from laboratory personnel or others who can perform D_{LCO} maneuvers on a routine basis.¹ The Clinical and Laboratory Standards Institute (CLSI) states that control materials should have an established target mean and SD and recommends 10 measurements made on separate days to establish the *initial* target value.³ The 2017 ATS/ERS D_{LCO} standards do not specify how to establish the target mean D_{LCO} but imply technologists can use the mean of 6 values. The standards provide limited guidance for the second QC strategy step, establish expected values for control materials. Established values need both accuracy and precision. Scientists use the coefficient of variation (CV) to assess precision when the measurement's mean and SD depend upon each other in a single sample⁴ and the root mean square CV (RMSCV) to estimate a population's precision.⁵ A defined CV assures that

measurements for D_{LCO} BioQC occur in an expected range, confirming the D_{LCO} system is in-control and the BioQC performed the procedure consistently.⁴

Several studies of D_{LCO} data from healthy subjects found a CV or RMSCV ranging from 5–10%.^{6–9} These studies employed a variety of time frames, laboratories, testing systems, along with various levels of technologist experience and technical oversight as shown in Table 1. A separate study explored the target mean D_{LCO} by using either a single value, the mean of 6 values, or mean of all values after assuring the equipment passed D_{LCO} simulator testing with QC oversight. Study data utilized the mean of the first 2 acceptable efforts that varied by $\leq 15\%$. The authors concluded the first 6 values established an appropriate mean.¹⁰ Most PFLs lack D_{LCO} simulator equipment and access to external QC oversight to assure accuracy. Therefore, technologists unknowingly using inaccurate equipment could establish an errant mean D_{LCO} in the absence of a defined CV that assesses the control's expected values.

Next, QC programs need to establish control rules to identify out-of-control conditions. The Association for Respiratory Technology and Physiology (ARTP) recommends computing control limits using the mean ± 2 SD,¹¹ which is consistent with guidelines from the CLSI.³ Additionally, blood gas QC programs use this strategy, making it familiar to clinicians.

The 2017 ATS/ERS D_{LCO} standards recommend an alternative BioQC control rule of mean $\pm 12\%$ of the D_{LCO} mean. This recommendation was based upon a single study with data derived from 162 different sites and included 288 BioQCs without self-reported lung disease that could be a current or past smoker. Data were collected from 6 months–5 y and only included one equipment brand for measuring D_{LCO} . The researchers found a mean intersession variability of 12.3% at the 90th percentile.¹⁰

The 2017 ATS/ERS D_{LCO} standards lack a measure of precision to confirm that measurements used in control rules occur in an expected range and thus fail to confirm that the system is in-control before computing a BioQC's

QUICK LOOK

Current knowledge

The 2017 American Thoracic Society/European Respiratory Society (ATS/ERS) diffusing capacity of the lung for carbon monoxide (D_{LCO}) standards recommend conducting weekly biologic quality controls (QCs) (BioQCs) but do not specify how to establish the BioQC's target mean D_{LCO} . Further, the standards do not specify coefficient of variation (CV) values to confirm control rule measurements are derived from an expected range.

What this paper contributes to our knowledge

Technologists can achieve a CV $\leq 6\%$ for the initial D_{LCO} BioQC mean across a wide range of sites, personnel, and equipment. The mean ± 2 control rule appears to provide similar results as the mean $\pm 12\%$ of the mean control rule recommended in the 2017 ATS/ERS D_{LCO} standard.

target mean D_{LCO} . Further, the control rule of mean $\pm 12\%$ of the mean in the 2017 ATS/ERS D_{LCO} standards was based upon a single study,¹ but the mean ± 2 SD control rule is being used in guidelines¹¹ and clinical practice. Therefore, this study's first aim was to establish the precision for expected values in D_{LCO} biologic control materials using CV. The second aim compared two control rule methods, using the mean ± 2 SD with the 2017 ATS/ERS D_{LCO} standards mean $\pm 12\%$ of the mean.¹

Methods

This descriptive study was a secondary analysis of data collected as part of a large, global pharmaceutical study, NCT02242487. The BioQC data were collected over the course of 42 months, concluding in 2018. The D_{LCO} was measured in 217 BioQC participants from 114 PFLs located in North America, Europe, and Israel. Five manufacturers of D_{LCO} equipment were included. This study received institutional review board approval from Rush University Medical Center, Rush University, Chicago, Illinois, ORA number 19032007.

On-site training was provided to all sites by 5 prequalified trainers with > 10 y of experience in PFLs. Additionally, trainers held Registered Respiratory Therapist (RRT) and/or Registered Pulmonary Function Technologist (RPFT) credentials or equivalent based upon residing country. Training included verification of D_{LCO} equipment settings, medical gas accuracy, test method, and equipment function. Acceptable syringe D_{LCO} check and D_{LCO} simulation studies with Hans Rudolph D_{LCO} Simulator with EasyLab Software (Hans

Dr Becker is affiliated with Rush University Medical Center, Chicago, Illinois. Ms Moran (now retired) was affiliated with Rush University Medical Center, Chicago, Illinois. Mr Blonshine and Ms Blonshine are affiliated with TechEd Consultants, Mason, Michigan.

Ms Blonshine and Mr Blonshine disclose relationships with Acorda Therapeutics. The remaining authors have disclosed no conflicts of interest.

Correspondence: Ellen A Becker PhD RRT RRT-NPS RPFT AE-C FAARC, 600 S Paulina St, Suite 765, Chicago, IL 60612. E-mail: Ellen_Becker@rush.edu.

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BIOLOGIC QUALITY CONTROL FOR D_{LCO}

Table 1. Diffusing Capacity of the Lung for Carbon Monoxide Coefficient of Variation and Root Mean Square Coefficient of Variation Findings in 4 Longitudinal Studies

Characteristic	Gochicoa-Rangel et al ⁶	Hathaway et al ⁷	Jensen et al ⁸	Wise et al ⁹
No. of laboratories	1	3	5	33
No. of equipment brands	1	3	5	1
Sampling time frame	3 y	1 y	6 mo	24 wk
No. of biologic controls	1	8	8	196
Documented training	No	No	Yes	Yes
Central oversight of results	No	No	No	Yes
Measure of variability and results	CV (%) EasyOne Pro: 5.4	CV (%) Collins: 4.74 Systems Research Laboratories: 4.84 Gould: 6.83	RMSCV (%) Collins: 4.43 JAEGER: 5.79 Med Graphics: 9.83 Morgan: 9.36 Sensor Medics: 6.48	RMSCV (%) Collins: 6.01

CV = coefficient of variation
RMSCV = root mean square coefficient of variation

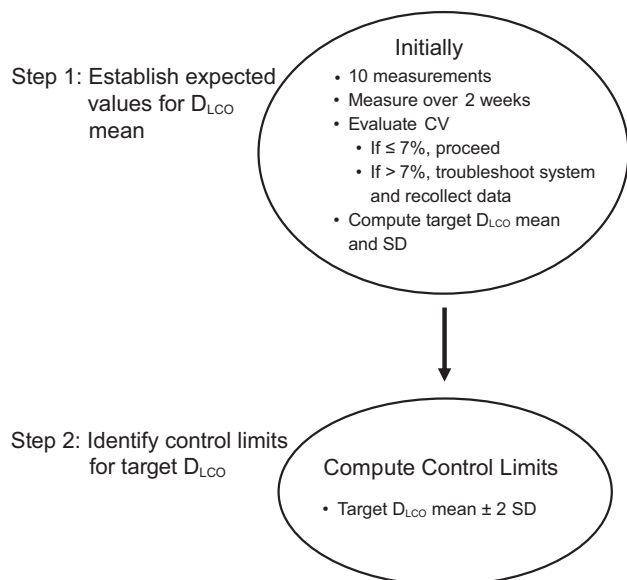


Fig. 1. Conceptual framework for establishing the study's initial target diffusing capacity of the lung for carbon monoxide biologic quality control values and control limits. D_{LCO} = diffusing capacity of the lung for carbon monoxide; CV = coefficient of variation.

Rudolph, Shawnee, Kansas) were confirmed prior to BioQC test performance. Simulation data were in-control when D_{LCO} variables (D_{LCO} , inspiratory vital capacity, alveolar volume, expired carbon monoxide, and expired tracer gas concentrations) were within 10% of the expected values. Each trainer completed slow vital capacity and D_{LCO} measurements as a mock BioQC subject during the site training to confirm the technologists' adherence to the 2005 ATS/ERS D_{LCO} standards¹² and consistent results between the trainer's D_{LCO} result and historical values. BioQC data including spirometry and D_{LCO} were submitted weekly for central review throughout

the study. Data collection was not controlled for diurnal variation as assessment for a suspected out-of-control situation can occur at any point in the day. Reviewers with 10–40 y of experience and RRT and/or RPFT credentials used a standardized process to evaluate the data. BioQC data were accepted if calibration, syringe D_{LCO} check, and D_{LCO} simulations were in-control and met the 2005 ATS/ERS test performance and repeatability standards.¹² The first two acceptable and repeatable D_{LCO} trials were averaged.

The conceptual model used for this study appears in Figure 1. Sites submitted 10 d of BioQC testing to evaluate whether the measurements met an expected $CV \leq 7\%$. If the initial CV was $> 7\%$, troubleshooting was completed, and an additional 10 d of BioQC data were collected. Demographic data were extracted from reports for BioQC participants' age, sex, height, and weight.

All acceptable data were compiled in an Excel spreadsheet (Microsoft, Redmond, Washington), and BioQC values within 5 d were deleted to allow for variability. Measures taken over a few months provide better estimates of SD as they integrate the changes that occur with environmental factors, routine maintenance, and other sources of variation such as physiology.³ Analysis was conducted on individuals where there was a minimum of 10 D_{LCO} BioQC measures within a 12-month period. A CV was computed for each participant for each year of data using the first 10 measurements meeting the criteria described above by dividing the SD into the mean. Next, we computed an average CV value for each year's subjects using RMSCV as shown in Equation 1. When pooling precision data for a group, the best unbiased estimate of the population variance is SD^2 and not SD .^{5,13} Thus, we squared each CV, averaged the squared values, then computed the square root to generate the RMSCV.

Table 2. Demographic Data*

Demographic Variables	Year 1 (n = 168)	Year 2 (n = 89)	Year 3 (n = 28)
Sex			
Female	110 (65.5)	56 (63)	14 (50)
Male	53 (31.5)	32 (36)	14 (50)
Missing	5 (3)	1 (1)	0
Age, y			
Mean ± SD	46.3 ± 13.3	46.7 ± 12.8	50.5 ± 4.6
Range	20–73	21–73	45–60
Height, cm			
Mean ± SD	169 ± 8.9	169 ± 9.6	168 ± 10.8
Range	152–191	152–191	152–182
Weight, kg			
Mean ± SD	77.5 ± 17.7	75.5 ± 16.4	78.5 ± 16.9
Range	42–142	42–110	42–105
D _{LCO} , mL/min/mm Hg			
Median (IQR)	23.6 (20.4–29.8)	23.1 (19.8–29.8)	26 (20.1–30.4)
Range	12.9–43.2	15.2–43	15.9–39

Data are presented as n (%) or median (interquartile range) unless otherwise indicated.

* Several variables had incomplete data.

D_{LCO} = diffusing capacity of the lung for carbon monoxide

IQR = interquartile range

$$RMSCV = \sqrt{\frac{\sum_{i=1}^n CV_i^2}{n}}$$

where CV_i is the CV of an individual BioQC and n = the total number of subjects in the year.

Additionally, the control limit in the 2017 ATS/ERS D_{LCO} standard, which was ≤ 12% of the mean,¹ was compared with the 2 SD control limit in the current study. Therefore, this study’s control limit of 2 SD was divided by the mean as indicated in Equation 2 to allow direct comparisons between studies.

$$\frac{2 \times SD}{\bar{x}} \times 100$$

where SD = standard deviation and \bar{x} = the D_{LCO} mean, both from the first 10 values of each year.

Data Analysis

Descriptive statistics characterized demographic variables, D_{LCO}, CV, and RMSCV for each year of participation. We tested the relationship between each year’s D_{LCO} mean and SD through Spearman rho or Pearson r based upon the distribution’s normality. Additionally, Friedman test evaluated the intra-subject variation in CV across the 3 y using α = 0.05. The 90th percentile was computed for each year’s 2 SD control limit’s percentage of mean D_{LCO} to directly compare this study’s results with the 90th percentile values from

a prior study.¹⁰ Data analysis was performed using SPSS Version 26.0 (IBM, Armonk, New York).

Results

Data from 217 participants were reviewed, of which 168 (77%) completed 10 or more D_{LCO} BioQCs their first year and 89 (41%) and 28 (13%) for years 2 and 3, respectively. Most participants were female (65.5%) with a mean age of 46.3 y and median D_{LCO} of 23.6 mL/min/mm Hg. D_{LCO} equipment from 5 manufacturers was included: Vmax (Vyaire Medical, San Diego, California), n = 67, 39.9%; ndd EasyOne Pro (ndd Medical Technologies, Andover, Massachusetts), n = 34, 20.2%; Jaeger (Vyaire Medical, San Diego, California), n = 29, 17.3%; MGC Diagnostics Corporation (St. Paul, Minnesota), n = 29, 17.3% ;and KoKo - formerly NSpire Health (Longmont, Colorado), n = 9, 5.4%. Complete demographic data appear in Table 2.

Moderate correlations emerged the first 2 years between the mean and SD with r_s = 0.503, P < .001, n = 168; r_s = 0.493, P < .001, n = 89; and r = 0.373, P = .051, n = 28 in years 1, 2, and 3, respectively. The median CV for D_{LCO} BioQC was near 4%, and the RMSCV values were consistently < 6% across all years. These data are summarized in Table 3. Friedman test confirmed there was no variation in CV (medians 4.33, 3.76, and 3.38% for years 1, 2, and 3, respectively) for the 24 participants with data for all 3 y, Q = 5.25, degrees of freedom = 2, n = 24, P = .07. The discrete data from all participants over 3 y appear in Figure 2.

Table 3. Coefficient of Variation for Diffusing Capacity of the Lung for Carbon Monoxide Biologic Quality Control Over 3 Years

	<i>n</i> BioQC Subjects	CV% Median	CV% Range (IQR)	RMSCV%
Year 1	168	4.83	1.79–11.06 (3.80–5.95)	5.3
Year 2	89	4.03	1.73–10.23 (3.00–5.09)	4.5
Year 3	28	3.52	0.65–13.28 (2.90–4.87)	4.6

BioQC = biologic quality control
 CV = coefficient of variation
 IQR = interquartile range
 RMSCV = root mean square CV

The control limit's percentage of D_{LCO} mean was computed for each year. The resulting 90th percentile values were 15, 12.4, and 11% for years 1, 2, and 3, respectively.

Discussion

This study showed that a $CV \leq 6\%$ establishes the expected precision for D_{LCO} biologic control materials among a diverse population of subjects, sites, and equipment. Moderate correlation between the mean and SD D_{LCO} measures supported the use of CV to assess precision. The CV values remained stable over the course of the study. Further, this study's mean $D_{LCO} \pm 2$ SD control rule yielded

similar results as the mean $\pm 12\%$ of the mean control rule recommended in the 2017 ATS/ERS D_{LCO} standards.

Ideally BioQCs achieve low CV values to limit the amount of equipment and procedural error that could impact each person's test results. Lower CV values can be obtained by a single individual testing using the same brand of equipment in the same lab. A retrospective observational study of persons referred to a university clinic evaluated intra-session D_{LCO} . Subjects with normal lung function ($n = 821$) had a $CV = 3.09\%$.¹⁴ Another study ($n = 1$) had a healthy BioQC test weekly for 3 y with the same instrument and yielded a $CV = 5.4\%$.⁶ Studies including multiple laboratories (3, 5, and 33 laboratories) yielded higher CVs near 5.0,⁷ 4.5–9.8,⁸ and 6.0%,⁹ respectively. The highest CV range occurred in the study that included the most diverse equipment. The current study's CV falls in a similar range as prior studies but is notable for achieving this relatively low value despite a greater number of laboratories, 5 different equipment brands, and diverse geographic locations. Thus, a $CV \leq 6\%$ should be achievable for all laboratories given the RMSCV findings from years 1–3. The Canadian Diagnostic Accreditation Program standards¹⁵ use a BioQC D_{LCO} $CV \leq 5\%$. This lower CV likely resulted from employing QC practices with test quality oversight and mentoring for many years. Thus, tighter control values could be consistently achieved in a single laboratory and potentially improve earlier detection of equipment errors.

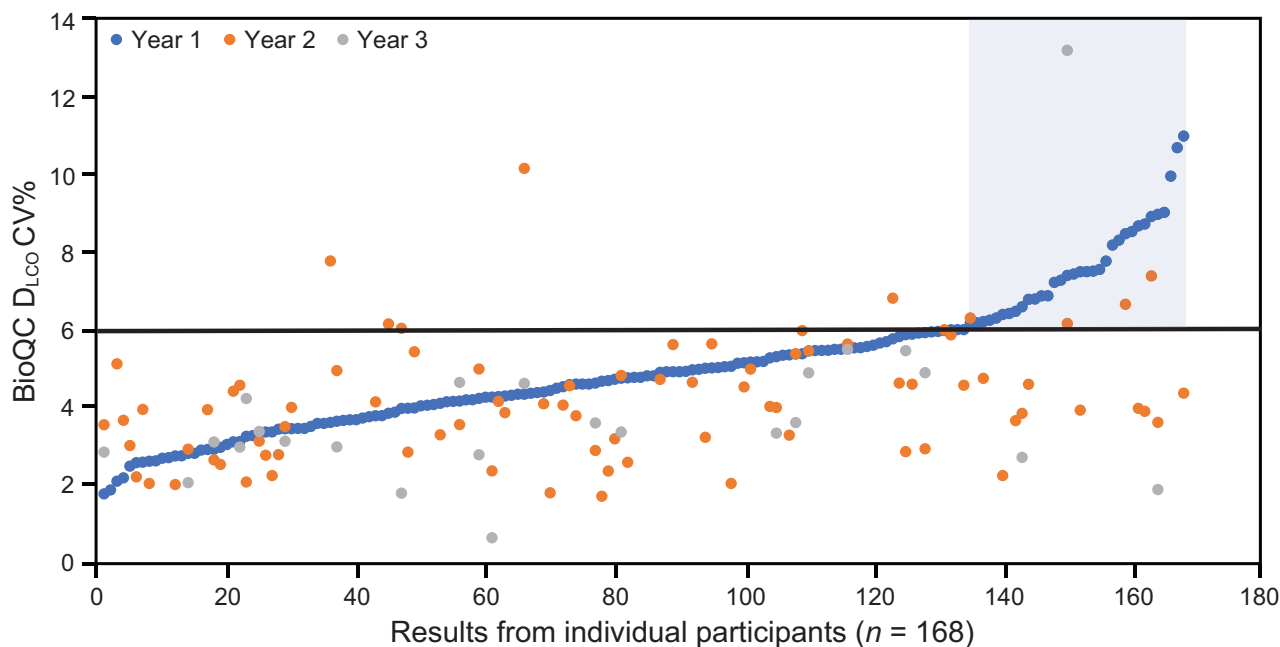


Fig. 2. Each dot represents a diffusing capacity of the lung for carbon monoxide coefficient of variation (CV) measurement from a participating biocontrol. The blue dots show results from the first year arranged in ascending order. Data from subsequent years are included when present. The blue shaded area highlights those participants who could not achieve a $CV \leq 6\%$. Most CV measurements for the second and third years were lower than the biocontrol's first year value. BioQC = biologic quality control; D_{LCO} = diffusing capacity of the lung for carbon monoxide; CV = coefficient of variation.

The stability of the CV over time has been questioned. This study and one other using SD to assess variability¹⁰ showed a lack of significant change over 3 or more years. Only 24 subjects in the current study had sufficient data for a 3-y comparison. These subjects had median CVs $\leq 4.3\%$ across all 3 y, suggesting they had experience to effectively maintain their equipment. Figure 2 also shows the impact of experience. Note that most persons with a high CV in year 1 were able to decrease their values in years 2 and 3. Thus, there appears to be a trend toward lowering CV with experience; however, our data did not permit us to confirm this observation with statistics. In any case, technologists should strive to achieve the lowest CV possible and re-evaluate their values annually.

The 2017 ATS/ERS D_{LCO} standards were not clear about how to establish the mean D_{LCO} . Both CLSI³ and ARTP¹¹ recommend that in the absence of historical QC data 10 measurements on separate days create a reasonable initial mean. However, use of measurements made over the first several months gives a better estimate because it accounts for longer-term sources of variability.³ In this study, a CV $> 7\%$ prompted a review of the technical procedure and/or equipment for error correction. Using a measure of precision to establish an expected value combined with consistent feedback from central review likely influenced the relatively low CV (5%) across the study.

After establishing the expected values, technologists create control rules to determine out-of-control conditions. QC rules should result in a low false-positive rate while detecting large enough error conditions that affect patient care decisions.³ The ARTP 2020 standards¹¹ and McCormack¹⁶ recommend using the mean ± 2 SD as the control rule. The second aim of this study was to compare the use of ± 2 SD from the mean as an equivalent control rule to the current 2017 ATS/ERS D_{LCO} standards. The 2017 standards were based upon a study that found values at the 90th percentile differed from the mean by 12.25% when the mean was an average of the first 6 measurements. The difference from the mean fell to 10.91% at the 90th percentile when the mean was an average of all measurements.¹⁰ Our data using 2 SD from the mean from years 2 and 3 were similar to the Hegewald et al¹⁰ study with values 12.4% and 11%, respectively, at the 90th percentile. Thus the control rule mean ± 2 SD in the current study appears to be consistent with prior work while using a familiar QC method.

Personnel who perform BioQCs may have concerns about their test results being a violation of their medical privacy. Thus, affordable mechanical devices to accomplish the QC goal would be beneficial. A D_{LCO} simulator verifies the accuracy and precision of the D_{LCO} system, and its use allows early detection of instrumentation problems. For example, at the start of an inhaled insulin study, 25% of study sites failed a D_{LCO} simulator test. However, simulator testing does not address procedural or patient

variability. Patients can account for 30–60% of intra-subject variability.¹⁷ One study found that BioQC was as good as a D_{LCO} simulator.⁶ This study, however, was conducted with a single machine and biologic control. Further, research is needed to clarify whether BioQC alone is sufficient.

Although QC practices were implemented in some research studies for the past 20 years, they remain underutilized in clinical PFL testing.¹⁸ One pharmaceutical study tracking the training intensity needed for conducting mechanical QC (syringe loops, syringe D_{LCO} , and D_{LCO} simulations) and BioQC showed poor understanding of QC procedures.¹⁹ In another study of 15 PFLs, most did not have standardized BioQC procedures, and initially 43% of the machines had unacceptable accuracy.²⁰ Technologists need to utilize principles of measurement science in their QC practices. The CLSI (<https://clsi.org/>. Accessed February 15, 2023) provides a well-established framework and vocabulary to guide QC in laboratory practices. These CLSI standards need to be integrated into laboratory education to assure test results accurately reflect patients' physiology, which may guide better treatment decisions, further drug development, or measure the impact of occupational exposures.

Methods for decreasing variability in D_{LCO} have been reported in multiple studies. These include using a D_{LCO} simulator,^{6,17,20,21} same brand of PFT equipment,^{6,7,9,22} standardizing test protocols,^{9,10,22} providing staff education with a written test and return demonstration,^{9,10,22} and review of D_{LCO} results at a centralized site with feedback.^{9,10,22} Numerous authors strongly endorse a central PFT test oversight with technologist feedback as a vital part of a quality assurance program.^{9,10,16,18,22-27} Use of oversight practices reduced variability in this study and two others.^{9,22} Not all countries have centralized test oversight by an accreditation organization. A senior technologist using a standardized process can perform this important duty in a single lab or health care system.

Technologists must be aware of other sources of D_{LCO} variability such as the technologist-subject interaction, circadian rhythms, potential underlying lung disease, fluctuating hemoglobin values, and the unique testing procedures imposed by different devices.⁸ Also, variability due to ambient environment must be considered for barometric pressure, relative humidity, and room temperature. Temperature alone will cause 0.67% error in D_{LCO} for every 1°C increase.¹⁶ One study found 36–70% of the D_{LCO} variability were due to instrumentation errors.²¹ Clinicians should not forget that reducing variability ultimately results in improving patient care.²⁸ A suggested D_{LCO} QC checklist for QC appears in Table 4.

To move QC into the forefront of diagnostic testing, QC education needs to be enhanced in both training programs

BIOLOGIC QUALITY CONTROL FOR D_{LCO}

Table 4. Diffusing Capacity of the Lung for Carbon Monoxide Biological Quality Control Steps

1. Select appropriate control participant
 - a. Identify healthy biocontrol
 - Nonsmoking
 - No known lung disease
 - Available for QC testing schedule and troubleshooting
 - Performs acceptable and repeatable D_{LCO} tests
2. Ensure equipment is in-control for syringe linearity and syringe D_{LCO}
 - a. Verify mechanical dead space is set correctly in the system
 - b. Verify test gas gases meet manufacturer specifications (generally primary grade)
3. Assess initial CV for biologic control
 - a. Conduct 10 D_{LCO} tests meeting acceptability and repeatability standards on separate days
 - b. Evaluate variability of measurements through CV
 - If $CV > 6\%$
 - Troubleshoot equipment (see tips below)
 - If there were *no* equipment problems
 - Ensure BioQC was healthy during measurements
 - Consider another healthy BioQC
 - If an equipment problem was resolved
 - Gather an additional 10 tests from separate days and recompute the CV on the most recent 10 tests
 - If $CV \leq 6\%$
 - Appropriate to set initial control range based on D_{LCO} mean

Caution:

 - Measurements taken close together (daily) have the potential to create a low CV
 - Ten additional days of QC may be needed to reflect normal variation but still have $CV \leq 6\%$

Troubleshooting tips:

 - Verify dead space (system and physiologic) was entered accurately
 - Check environmental variables: barometric pressure, relative humidity, room temperature
 - Assess flow sensor, demand valves, balloon valves, and calibrating gas accuracy
 - Look for system leaks
 - Evaluate testing procedure competency
4. Set the D_{LCO} control range for each person on each instrument (see worked example on next page)
 - a. Mean \pm 2 SD or
 - b. Mean \pm 12% of the mean
5. Re-evaluate CV annually
6. Recover out-of-control conditions
 - a. Inspect equipment, test gas supply, environmental data input, spirometer, and gas calibrations; correct problem and retest
 - b. Test alternate BioQC
 - c. Call biomedical and/or manufacturer support group if out-of-control results continue
 - d. Remove equipment from service; do *not* test patients with out-of-control equipment
7. Document QC program outcomes (CLSI requirement)
 - a. Create spreadsheet to track data over time
 - AARC Respiratory Diagnostics Specialty Section has templates
 - b. Identify a person responsible for monitoring and reporting QC data
 - c. Identify a frequency for assessing the laboratory's QC outcomes
 - Annually or semi-annual review for mean, SD, and CV measurements
 - Monitor and report rate of QC rules rejections, root cause, and corrective action taken
 - Monitor and report results if there are procedure, equipment, and/or software/hardware changes

Technologist support resources

- AARC Respiratory Diagnostic Specialty Section
- Most recent ATS/ERS D_{LCO} Technical Standards
- ATS Pulmonary Function Procedure Manual
- Pulmonary function textbooks
- Manufacturer's operator manual
- Manufacturer representative and support group
- Institution's biomedical personnel

(Continued)

Table 4. Continued

Worked Example:

	Person 1 D_{LCO}	Person 2 D_{LCO}
	17.20	15.82
	17.57	16.30
	18.20	16.60
	18.20	16.67
	18.41	16.90
	18.48	17.00
	20.69	17.30
	21.16	17.63
	22.66	18.02
	23.17	18.18
Mean	19.6	17
SD	2.2	0.8
CV	11.1	4

Interpretation:

Assessment of CV

The CV for Person 1 is $> 6\%$. Troubleshoot the equipment and test performance prior to establishing the target mean

The CV for Person 2 is $\leq 6\%$. Therefore, establish a control rule based upon the target mean ± 2 SD or mean $\pm 12\%$ of the mean

Establish D_{LCO} Control Range

Person 1:

No control range was established because the CV was $> 6\%$

Person 2:

Control range was established because the CV was $\leq 6\%$

Control rule using mean ± 2 SD: acceptable values are 15.5–18.5 units ($17 \pm [2 \times 0.75]$)

Control rule using mean $\pm 12\%$ of the mean: acceptable values are 15–19 units ($17 \pm (0.12 \times 17)$)

QC = quality control

D_{LCO} = diffusing capacity of the lung for carbon monoxide

CV = coefficient of variation

BioQC = Biologic quality control

CLSI = Clinical and Laboratory Standards Institute

AARC = American Association for Respiratory Care

ATS/ERS = American Thoracic Society/European Respiratory Society

and clinical settings. Additionally, manufacturers could assist by creating device software to help monitor and generate BioQC data with flags for out-of-control BioQC results. Also, regulatory oversight would require that all PFLs meet quality standards and enable better patient care decisions.

Limitations

This study had several limitations. Variation for sex and age was weak due to majority of participants being female (65%) with a mean age of 46.3 y. Also, there was a decline in the participation numbers each year due to normal attrition and study closure. The CV remained stable across 3 years; however, the subjects included in the analysis had a lower mean CV than the whole population and could have been more experienced to achieve this lower CV. Thus, the impact of changing CV among lesser experienced technologists remains unanswered. Lastly, this study used the 2005 ATS/ERS D_{LCO}

standards;¹² however, the use of 2017 ATS/ERS D_{LCO} standards¹ would not likely increase the CV.

Conclusions

Health care providers need accurate data to deliver the best possible patient care. Thus, D_{LCO} QC standards need sufficient rigor to reflect the presence or absence of a diffusion defect. A D_{LCO} BioQC CV $\leq 6\%$ is achievable across multiple sites, multiple technologists, and different equipment brands. Evaluating the CV assures systems are in-control prior to establishing a control rule based upon a target D_{LCO} mean. It does not appear to matter whether the control rule for out-of-control status is the mean $\pm 12\%$ of the mean or the mean ± 2 SD as the results from both methods were similar.

The relatively low CV in this study was achievable because systems underwent troubleshooting whenever a BioQC had a CV $> 7\%$ with a team of experts who provided training and ongoing monitoring. Laboratory oversight by qualified personnel has been shown to improve D_{LCO} precision.

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