Facing the Noise: Addressing the Endemic Variability in D_{LCO} Testing

Meredith C McCormack MD MHS

Single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) is a common pulmonary function test that measures the ability of the lung to exchange gas across the alveolar-capillary interface. D_{LCO} testing is used to narrow the differential diagnosis of obstructive and restrictive lung disease, to aid in disability and transplant assessment, and to monitor medication toxicity. The variability in the measurement limits the utility of the test. Variability is attributable to differences in equipment, testing conditions, patient factors, and reference equations. Laboratories can minimize variability by ensuring that equipment meets recommended standards, implementing effective quality control programs, standardizing testing conditions and testing procedures, and accounting for pertinent patient characteristics. *Key words: pulmonary function; diffusing capacity; quality control; carbon monoxide; lung function.* [Respir Care 2012;57(1):17–23. © 2012 Daedalus Enterprises]

Introduction

Single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}), also referred to as the carbon monoxide transfer factor (T_{LCO}), measures the ability of the lung to transfer gases across the alveolar-capillary interface. This is the only pulmonary function test that does not measure lung mechanics. The D_{LCO} measurement reflects features of the resident alveolar gas, cell membranes, cytoplasm,

Dr McCormack is affiliated with the Department of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland.

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Correspondence: Meredith C McCormack MD MHS, Pulmonary and Critical Care Medicine, Johns Hopkins University, 1830 East Monument Street, 5th Floor, Baltimore MD 21205. E-mail: mmccor16@jhmi.edu.

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and hemoglobin binding, and is highly dependent on pulmonary blood volume.

The D_{LCO} is calculated using the following fundamental equation:

$$D_{LCO} = \dot{V}_{CO}/(P_{ACO} - P_{cCO})$$

Where $\dot{V}_{CO}$ is the rate of disappearance of CO, P_{ACO} is the average partial pressure of CO in alveoli, and P_{cCO} is the average partial pressure of CO in the pulmonary capillary plasma. As carbon monoxide (CO) has a high affinity for binding to hemoglobin and is present in very low concentrations in the plasma, P_{cCO} is essentially zero and the final equation is:

$$D_{LCO} = \dot{V}_{CO}/P_{ACO}$$

The D_{LCO} is highly dependent on both the properties of the alveolar-capillary interface and pulmonary capillary blood volume. Conceptually, this is demonstrated by 2 conductance properties: membrane conductivity (D_M), which reflects the diffusion properties of the alveolar-capillary interface, and the binding of carbon monoxide (CO) and hemoglobin (Hb). The carboxyhemoglobin (COHb) binding can be represented as the product of the CO-Hb chemical reaction rate (θ) and the blood volume in the alveolar capillaries (V_c). As the conductances are in series, the properties are related by:

$$1/D_{LCO} = (1/D_M) + (1/\theta V_c)$$

Indications for D_{LCO} Testing

D_{LCO} is used clinically to narrow the differential diagnosis in both restrictive and obstructive lung diseases. It can be important in the evaluation of transplant candidacy and disability assessment. D_{LCO} is also used to assess for medication toxicity and to follow the course of diseases, such as interstitial lung disease and COPD, over time. D_{LCO} measurements have been linked to the likelihood of requiring oxygen at rest and with activity across a variety of disease states[1–9] and have been shown to have prognostic value.[10,11]

Accuracy and reproducibility of the test are important features, especially considering the broad application of D_{LCO} testing in the initial and ongoing assessment of lung disease. High variability, both within and between laboratories, has been a limitation of D_{LCO} testing. Sources of variability include equipment, software, test gases, reference equations, testing procedures, and atmospheric conditions. Patient characteristics are also a source of variability. One goal of an effective quality control program is to limit this variability by optimizing accuracy and reproducibility.

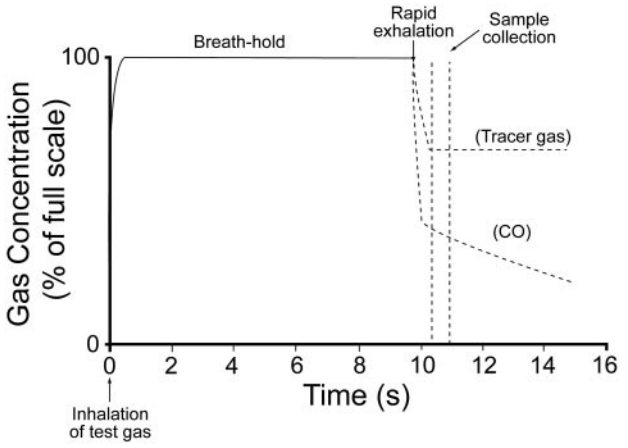

Fig. 1. A schematic representation of the diffusing capacity of the lung for carbon monoxide (D_{LCO}) maneuver, depicting the gas concentrations over time. The sampling period occurs between the 2 vertical dashed lines after the dead-space washout. (From Reference 12, with permission.)

Testing Procedures

The single-breath D_{LCO} maneuver is relatively simple. After a short period of tidal breathing, the patient inhales a vital capacity breath of test gas containing a small known concentration of CO and a known concentration of tracer gas, such as helium, methane, or neon (Fig. 1).

According to the American Thoracic Society/European Respiratory Society (ATS/ERS),[12] several criteria must be met for a test to be considered *acceptable*. The breath-hold time must be between 8 and 12 seconds, without evidence of leaks, Valsalva, or Müller maneuvers; the inspired volume must be greater than 85% of the largest vital capacity; the inspiration and expiration must each occur in less than 4 seconds and must be reached within 4 seconds. The sample collection time should be less than 3 seconds, with appropriate clearance of dead-space volume. Failure to meet any of these criteria (Fig. 2) has the potential to greatly impact test results. For example, taking a submaximal inspiration will result in an underestimation of the D_{LCO}, due to a smaller measured alveolar volume and also due to lack of recruitment. An inadequate breath-hold time will also underestimate D_{LCO}, while a leak in the system can result in an overestimation of the D_{LCO}.

The number of tests can influence results, as circulating COHb increases slightly with each trial. COHb reduces D_{LCO} by increasing CO back pressure and by decreasing the available hemoglobin binding sites for CO binding. On average, 5 tests will increase CoHb by 3.5% and thereby decrease measured D_{LCO} by 3–3.5%.[12] For this reason, it

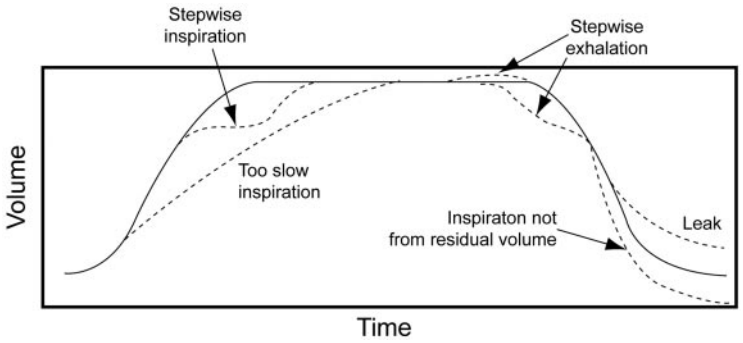

Fig. 2. Common potential sources of error that can occur with the diffusing capacity of the lung for carbon monoxide (D_{LCO}) maneuver. These include a stepwise inhalation or exhalation, a leak in the system, and an exhaled volume that exceeds the inhaled volume. (Adapted from Reference 12, with permission.)

is recommended that no more than 5 tests be performed in a single session, with a minimum of 4 minutes between tests to eliminate the tracer gas. Longer intervals should be considered in those with obstructive lung disease and slower emptying times.

To meet *repeatability* criteria, the test should be within 3 mL CO (standard temperature and pressure, dry [STPD])/min/mm Hg of each other or within 10% of the highest value.[12] The average of at least 2 acceptable tests (of the maximum of 5) that meet these criteria are then reported. These repeatability criteria are highly feasible to achieve. In a large university-based study, over 98% of tests met the current repeatability criteria. The percentage difference between the 2 tests was inversely related to the baseline D_{LCO} and FEV_1 while the absolute difference between repeat measurements was relatively stable, irrespective of the baseline values. These and other investigators have proposed a more stringent criteria, with the use of an absolute difference of 2–2.5 mL CO (STPD)/min/mm Hg).[13,14]

Equipment

Equipment is a source of variability between labs. In studies comparing 5 commercially available pulmonary function testing systems, there was substantial variability in the accuracy of the systems between manufacturers, with mean absolute accuracy in D_{LCO} ranging from 1 to 4.0 mL CO/min/mm Hg, and a cumulative change in the percentage of accuracy as high as 20% over a 90-day period.[15,16] In a study comparing patient versus instrument influence on variability by comparing maneuvers performed by biologic controls to those performed with a D_{LCO} simulator (Hans Rudolph, Shawnee, Kansas), instruments accounted for most of the observed variability (between 36% and 70%).[16]

The ATS/ERS statement on D_{LCO} testing outlines equipment specifications (Table 1).[12] Failure to meet these specifications introduces potential for inaccuracy. These include a volume accuracy within ±3% over an 8 L volume of test gases and gas analyzer linearity within ±0.5% of full scale, with stability over the duration of the test such that drift is less than ±0.5% of the measured gas. Circuit resistance should be less than 1.5 cm H_2O/L/s at 6 L/s flow. If a compressed gas source with a demand-flow regulator is used, the maximal inspiratory pressure through the circuit and valve should be less than 10 cm H_2O. The timing device should be accurate to within ±1.0%. The dead-space volume for the inspired gas and the alveolar sample should be known, and the dead space for the valve, filter, and mouthpiece should be less than 0.35 L for adult testing.

Table 1. Equipment Specifications for D_{LCO} Testing[12]

Volume accuracy	3% accuracy over an 8 L volume, using test gases (3.5% allowing for ±0.5% test syringe error)
Gas analyzers	Linear from zero to full span within ±0.5%; stable over test duration with drift < ±0.5% measured gas
Demand-valve sensitivity	< 10 cm H_2O required for 6 L/s flow through valve and circuit (if compressed gas source is used)
Circuit resistance	< 1.5 cm H_2O/L/s at a flow of 6 L/s
Dead-space volume	< 0.35 L for valve, filter, and mouthpiece
Timer	±1.0% over 10 s (100 ms)

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

Each requirement is important. As the D_{LCO} measurement relies on measurement of relative proportions of 2 or more gases, errors in gas analyzers have historically been an important source of variability in D_{LCO} measurement.[17,18] The advent of newer real-time gas analyzers has made it possible to measure smaller volumes of gas with faster response times. The graphical display enables evaluation of the tracer gas and CO concentrations throughout the testing period, with the opportunity to assess adequacy

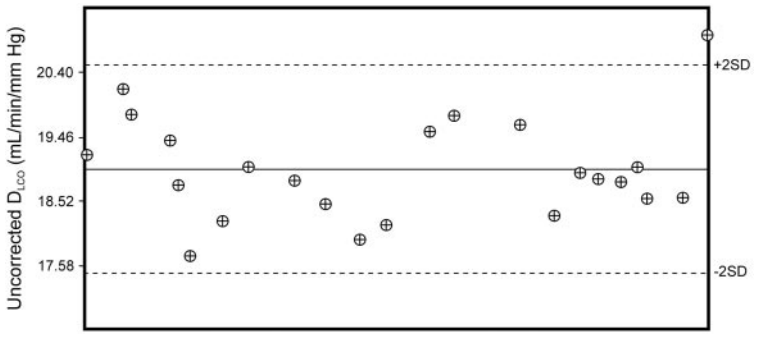

Fig. 3. A Levey-Jennings plot demonstrating D_{LCO} values obtained from a biologic control. Time is represented on the x axis, and D_{LCO} values are displayed on the y axis. The final data point on the far right exceeds 2 standard deviations above the mean. This is considered a "warning" condition that may indicate a problem with the system that warrants investigation. Mean = 18.99. SD = 0.76. Coefficient of variation = 4%.

of dead-space clearances by visual inspection. In a study that compared visual inspection to applying a set washout volume of 750 mL, visual inspection increased D_{LCO} values by an average of 4% and improved reproducibility from 89% to 94%. Thus, even though this approach is more labor-intensive and requires skill and training, visual inspection of gas tracings may improve reproducibility of D_{LCO} and may be especially beneficial in patients with low lung volumes.[12,19]

Atmospheric Conditions

The barometric pressure and temperature are both important considerations in D_{LCO} testing. While it is important for barometric pressure to be accurate on average, changes in temperature are more likely to influence D_{LCO} results. Each 1°C of error in temperature introduces 0.67% error in the D_{LCO}.[20] Thereby, temperature variations of 10°C that can occur during the course of a day can introduce almost 7% error in the measurement. Thus, accuracy of temperature measurement and frequency of measurements throughout the day are important to reduce error in the D_{LCO} measurement. Exhaled breath contains CO_2 and H_2O, which is removed in some systems to avoid interference with gas analyzer function. A common source of error is failure to exchange these chemical scrubbers after they have been exhausted. In these instances, the concentrations of CO and tracer gas will be altered, potentially influencing both the alveolar volume measurement and the gas transfer coefficient.

Quality Control Programs

Quality control programs are necessary to ensure that equipment continues to meet specifications over time, and more rigorous quality control programs have been shown to decrease inter-session variability of D_{LCO} testing.[21] Despite this, most laboratories have not implemented quality control programs. Equipment quality control recommendations include zeroing the gas analyzer prior to each test, daily assessment of volume accuracy, weekly biologic control or simulator testing, and assessment of the timer and gas analyzer linearity every 3 months. In survey of 73 United States pulmonary function laboratories, 26% reported that they never performed biologic control testing, and 37% reported that they never checked the volume accuracy of D_{LCO} equipment.[22]

Records of equipment checks and biologic control or simulator testing should be maintained and results plotted over time. A Levey-Jennings chart can be used to graphically display the D_{LCO} values obtained from the biologic control or simulator (Fig. 3). The date and time of testing are plotted on the x axis, data with the D_{LCO} values on the y axis, and horizontal lines delineate 1, 2, and 3 standard deviations from the mean. Westgard's rules can then be applied to determine "out-of-control conditions" that should prompt quality assurance responses, such as appropriate repair or replacement of equipment.[23,24] A simulator that uses precision mixed gases to simulate volumes and gas concentrations that would be measured from a human subject is now commercially available. A study using the D_{LCO} simulator investigated accuracy and precision of D_{LCO} systems and found as much as a 20% change in accuracy over time, translating to a change of about 4 mL/min/mm Hg in a person with an initial D_{LCO} of 20 mL/min/mm Hg.[15] Implementation of the weekly or biweekly simulator testing has been shown to improve accuracy of D_{LCO} equipment and to allow maintenance of accuracy over time in the setting of clinical trials.[23] The features of a quality control program are somewhat dependent on the size, staffing, and resources of the laboratory, but should be designed to at least meet the minimum standards outlined in the guidelines.[12,24]

Table 2. Patient Characteristics That Cause Low D_{LCO}

Restrictive lung disease (eg, interstitial lung disease)
Obstructive lung disease (eg, emphysema)
Pulmonary vascular disease (eg, pulmonary hypertension, pulmonary embolism)
Anemia
Increased carboxyhemoglobin (smoking)
Valsalva manuever

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

Table 3. Patient Factors That Cause Elevated D_{LCO}

Obesity
Asthma (normal to high D_{LCO})
Left-to-right shunt
Pulmonary hemorrhage
Polycythemia
Left heart failure
Exercise just prior to test
Müller maneuver
Supine position

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

Patient Factors That Influence D_{LCO}

Tables 2 and 3 show patient factors that influence D_{LCO}.

Disease State

D_{LCO} is typically performed to determine the influence of disease on resultant values. D_{LCO} is decreased in some obstructive lung diseases, such as emphysema, and in restrictive lung diseases, such as pulmonary fibrosis, sarcoidosis, and pneumoconiosis. Pulmonary vascular disease, such as pulmonary hypertension and pulmonary embolism, will also decrease D_{LCO}, and this may manifest as an isolated D_{LCO} abnormality. Increases in D_{LCO} are seen with obesity, pulmonary hemorrhage, and left-to-right shunt.[25] A normal to increased D_{LCO} occurs in asthma, obesity, and after surgical resection, as these all increase (relative) capillary blood flow. Anemia decreases measured D_{LCO}, and adjustments should be made for patients with anemia. Variation in D_{LCO} has been described in relation to the menstrual cycle in female patients,[26] and diurnal variation also occurs.[27]

Test Performance

In addition to the diseases that influence D_{LCO}, other patient characteristics can influence test results. Patients are typically tested in the seated position, using nose clips and a mouthpiece. Patients who have recently exercised or who are tested in the supine position will have elevated D_{LCO} values. The technique used to perform the D_{LCO} maneuver can alter results, as a Valsalva (forced exhalation against a closed airway) maneuver will decrease measured D_{LCO}, and a Müller (forced inhalation against a closed airway) maneuver will increase D_{LCO}, due primarily to changes in pulmonary blood volume. Smoking also increases COHb and decreases measured D_{LCO}. While healthy nonsmokers typically have very low COHB levels of less than 2%, smokers may have COHb levels greater than 10%. Each 1% increase in COHb causes an approximate 1% decrease in measured D_{LCO}. Patients should refrain from smoking 24 hours prior to the test, and if smoking occurs, this should be noted. A correction for CO back pressure should be made in those suspected of having a COHb of greater than 2%. Use of supplemental oxygen will decrease measured D_{LCO} by interfering with COHb binding, and, if possible, patients should rest without use of supplemental oxygen for 10 min prior to testing.

Considerations in Interpreting D_{LCO}

Reference Equations

In the most recent update of the ATS/ERS standards, there was no recommendation of a single prediction equation, due to the high inter-laboratory variability.[28] Unlike spirometry, for which there is a recommended set of reference equations based on a large sample population,[29] the available reference equations for D_{LCO}[30–34] are older and based on smaller sample populations. There is substantial variation in predicted values among the available reference equations.[35] In general, the choice of a reference equation should take into account methodologic differences (age and characteristics of the equipment), testing conditions (altitude), and the characteristics of the patients being studied. Predicted values for D_{LCO}, alveolar volume, and CO transfer coefficient (K_{CO}) should all be derived from the same source. Some reference equations include a body-weight term in predicting alveolar volume, which may be an increasingly important consideration with the rising prevalence of obesity.[33,34] There is a positive relationship between weight and D_{LCO}, meaning that D_{LCO} tends to increase as body weight increases. There may be gender differences in the relationship between body weight and D_{LCO}, as weight has been a significant predictor of D_{LCO} among women.[35] Proponents of including the actual weight as a term in the reference equation for predicted D_{LCO} emphasize the need to develop new reference equations in populations with a broader weight ranges.

As there is no single recommended D_{LCO} prediction equation, laboratories should choose equations based on their population and testing conditions, but this contributes

to the variability between laboratories. In interpreting D_{LCO}, if different reference equations have been applied (eg, from testing in different laboratories), this should be recognized and taken into account. Ultimately, development of new reference equations for D_{LCO} based on a large, representative sample of the population is needed.

Adjustments

Prior to interpreting D_{LCO} results, the quality of testing and any unique testing conditions should be reviewed. Adjustments to the measurement may be considered if the patient has anemia, has used supplemental oxygen, or has recently smoked. While the ATS/ERS guidelines recommend adjusting the predicted value, many laboratories adjust the measured value. Adjustment for alveolar lung volume is controversial.[28,36–38] The relationship between D_{LCO} and alveolar volume is complex; in normal lungs the D_{LCO} adjustment for a submaximal inspiration is not a 1:1 relationship and, therefore, simply dividing D_{LCO} by alveolar volume will result in "overcorrecting" and a supernormal corrected value. Furthermore, the relationship between D_{LCO} and alveolar volume varies by disease state and physiologic conditions. A better approach to interpreting D_{LCO} in the setting of abnormal lung volumes is to consider the pattern and clinical context rather than rely on a "corrected" value.[39]

Clinically Important Changes

In determining a clinically important change in D_{LCO}, consideration of the inherent variability in the measurement is important. The ATS/ERS guidelines currently state that a change of 10% or more should be considered clinically important. This recommendation is based on data from 8 healthy trained pulmonary function technicians collected over 1 year.[40] More recently it has been suggested that a 10% change may be too small to be considered clinically important, based on large clinical trials of inhaled insulin that assessed D_{LCO} in diabetics without overt lung disease.[21] Data from more than 1,500 participants demonstrated that quality control influenced inter-session variability in D_{LCO} measurements; using the 10% threshold, 15% of those who underwent repeated highly standardized testing and 35% of those who underwent repeated routine testing would be characterized as having a clinically important change despite no other evidence of change in lung function. Based on these findings, the authors proposed a threshold of 20–25% as more appropriate for determining a clinically important change. In fact, each laboratory must assess D_{LCO} variability using the available equipment and technicians and consider this variability in interpretation of results. At the individual level, differences in testing conditions should be considered when interpreting a clinically important change in a patient. These include factors such as whether testing was done at the same laboratory, with the same equipment, reference equations, and patient factors, such as use of oxygen, smoking status, and presence of anemia as examples.

Summary

Implementation of quality control practices improves accuracy and precision in D_{LCO} testing and can substantially reduce variability, cutting variability in half in some instances. These quality control measures include ensuring that equipment meets the recommendations of the ATS/ERS standards and implementing a quality control program that includes routine testing of equipment with a systematic approach to addressing out-of-range test results. Laboratories can also decrease variability by maintaining standard testing procedures and documenting changes in environmental conditions, such as ambient temperature, and patient conditions, such as the presence of supplemental oxygen, recent smoking, or anemia.

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Discussion

Coates: I have a comment and a plea, as well as a question. The comment and plea is that I chair a committee for the Canadian Thoracic Society, and we have recently requested that the next Statistics Canada's Canadian Health Measure Survey, which includes spirometry, also include D_{LCO}, because there's so much concern about the reference equations. I guess the plea would be that maybe Bruce Culver or other representatives from major organizations do the same thing with NHANES [National Health and Nutrition Examination Survey]. While we have excellent values for spirometry, there's nothing equivalent for D_{LCO}, and if I put on my pediatric hat (which I wear all the time), it is even worse for children. So if we can get our major survey organizations to include D_{LCO} testing and give them some guidance and help to make sure that they have accurate testing, I think it will go a long way in giving us better reference equations that will allow us to come up with decisions as to what's normal and what's abnormal instead of saying, "you're normal if we use this reference equation and you're abnormal if we use that."

The second question I have is, when you show that the repeatability of the measurement changes depending on how low the D_{LCO} is, how much of that is lung volume related? Again, with children we often get in the situation where we just don't have a VC [vital capacity] large enough to give

us a large enough sample volume to enable an accurate measurement.

McCormack: I think that's a good point. It is not clear how much of this is lung volume related.

Enright: You test children as well as adults in your lab, so did your repeatability study include children?

McCormack: No, this does not include children. This includes adults and it could include some late teens, but that would probably be a very small subset.

MacIntyre: As I run our clinical lab, D_{LCO} is used very heavily by our interstitial lung disease folks, and it's used very heavily by our oncologists, because they think this is a nice way to look for early lung toxicity. I'm struck that there are 2 common themes that I always get asked by these clinicians.

Number one is, what is a big enough difference to be a real difference? They're convinced 10% means something, and I think you've shown data that says that may be way too tight and you'll be calling something abnormal that is not. That's why I like to say at least two and a half units [units = mL/min/mm Hg] before you start getting excited about a difference. 10% of a D_{LCO} of 10 is only 1 and that is hardly, I think, a meaningful change.

The second issue that is quite pervasive, and you addressed it a bit, is this notion that you can somehow "correct" a low D_{LCO} for a low alveolar volume. As you pointed out quite correctly, the relationship of D_{LCO} and alveolar volume is not a straight line by any means. I think this relationship can help with the interpretation of diffusion. But to say that because your diffusing capacity was reduced by 50% and your lung volume's reduced by 50% (ie, that they went down the same), ergo the D_{LCO} is normal, is quite simply wrong. I see a lot of people in the clinical world getting caught in that trap saying, "Neil, I realize the D_{LCO} is down, but so's the lung volume, so everything's OK." I guess that really wasn't much of a question, but more of a comment and to thank you for bringing these points up.

Miller: Thank you for your stimulating presentation. Since I still have some green (old-fashioned spirometer pen) ink somewhere on a finger, I'd like to put this in perspective. If we look at the current D_{LCO} systems, compared to the 5-way valve you manually turned and the bag in the box you had to fill, I think we've come a long way. One of the big advances is the instantaneous CO and diluent gas analyzers, which permit you to see that you have indeed cleared the dead space. That eliminates a lot of the error, especially with smaller lung volumes, and mitigates the need to have a collection of 0.5 L or 1 L of gas to make measurements. I've been impressed that, for a test that includes so many variables, done by a human being, in which you're measuring volume and time and concentrations of at least 2 gases, how repeatable it is in most patients. Given the number of technical things you're paying attention to, I think getting the reproducibility to 5% or less (within 1 or 2 units) in successive tests is impressive.

On the question of smoking, I'd like to make a plea to the manufacturers (at least one of whom has a representative here) that it's very easy, since you have a CO analyzer in the test apparatus, to measure end-tidal CO and know indeed that a patient is still smoking and has recently smoked. We measured end-tidal CO routinely in many of our studies. To make that easily available in the lab will tell you that indeed this patient who says "I don't smoke" is still smoking and smoked recently before the test. This changes the test result from what it would otherwise be and raises the question of smoking-specific reference equations.

Pichurko: In centers with sizeable interstitial lung disease programs I'm sure it is widely appreciated that the diffusion capacity has a tremendous prognostic value in this population, when measured serially, and, in particular, along with FVC after one year's treatment. So accuracy is key, and the problems that we face involve measuring those people whose vital capacity has drifted below the 1-liter level. I wonder if anyone would care to share their experience with gas mixtures that have different kinetics, speedier kinetics than helium, along with rapidly responding gas analyzers in order to allow accurate and more reliable measurements at severely reduced lung volumes?

MacIntyre: I just want to make sure I even understand the question. One of the beauties of the rapidly responding meters that you were referring to is that they allow you to actually look at the tracings. I remember when these first came out, Tony Huang and I did a study[1] looking at that, and it was amazing: even following the ATS criteria, I think it was 7% or 10% of them still were not adequately clearing the dead space. It's almost a religion back home to make sure that the techs look at these tracings very carefully to make sure that we've cleared dead space.

And it works both ways, because it also means [that] when you've got someone with a very small VC you might actually be able to get away with a very small clearing volume and a very small sample volume. So I'm really pleased that these analyzers over the last 20 years have really changed things a lot. But I'm a little confused: you say agents other than CO. Are you referring to nitric oxide maybe?

1. Huang YC, MacIntyre NR. Real-time gas analysis improves the measurement of single-breath diffusing capacity. Am Rev Respir Dis 1992;146;(4):946-950.

Pichurko: Diluent gases with different kinetics.

MacIntyre: Like?

Pichurko: Methane, xenon.

MacIntyre: Oh, OK. Nitric oxide has certainly been discussed, our folks back home use xenon not so much as a diffusing measurement but as an MRI [magnetic resonance imaging] scanning agent, to look at gas distribution and gas transfer.

Coates: One of the challenges that we struggle with in pediatrics with variable VCs when we are doing the small children on equipment that was largely designed for adults, and using filters, there's a lot of dead space involved in the equipment. I would ask the manufacturers, if we could reduce that dead space, would we have more accurate values, since it would be easier to make sure we've washed out the physiologic dead space? I worry that there is a lot of noise that's introduced by the equipment dead space when testing small children.

Enright: Including those bacteria filters.

Coates: Yes. The bacteria filters have a considerable amount of dead space added and they certainly give rise to turbulence in mixing.