Standardisation of the single-breath determination of carbon monoxide uptake in the lung


KEYWORDS: Alveolar-capillary permeability, carbon monoxide, carbon monoxide diffusing capacity of the lungs, carbon monoxide transfer factor of the lungs, gas exchange, inspiratory manoeuvres

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BACKGROUND

This joint statement is based on the previous statements from the American Thoracic Society (ATS) and the European Respiratory Society (ERS), and much of the material was taken from these statements [1, 2]. It has been updated according to new scientific insights and revised to reflect consensus opinions of both of these societies. This document is meant to function as a stand-alone document, but, for certain issues, references will be made to the previous statements. Although there are other ways to measure carbon monoxide (CO) uptake (e.g. steady-state, intra-breath and rebreathing techniques) [3–9], the following recommendations will be restricted to the single-breath technique, since this is the most common methodology in use around the world.

The capacity of the lung to exchange gas across the alveolar-capillary interface is determined by its structural and functional properties [3–22]. The structural properties include the following: lung gas volume; the path length for diffusion in the gas phase; the thickness and area of the alveolar capillary membrane; any effects of airway closure; and the volume of blood in capillaries supplying ventilated alveoli. The functional properties include the following: absolute levels of ventilation and perfusion; the uniformity of their distribution with respect to each other; the composition of the alveolar gas; the diffusion characteristics of the membrane; the concentration and binding properties of haemoglobin (Hb) in the alveolar capillaries; and the gas tensions in blood entering the alveolar capillaries in that part of the pulmonary vascular bed which exchanges gas with the alveoli.

Definitions

The rate of CO uptake from the lungs is the product of alveolar partial pressure of CO in excess of any back pressure in the blood (the driving pressure) and a rate constant. This is for CO in the whole lung per unit of driving pressure. For practical reasons, using the single-breath method described below the CO uptake from the lung (KCO) is measured as a concentration fall in alveolar CO per unit time per unit CO driving pressure (PA,CO):

\[ K_{CO} = \frac{\Delta[CO]}{\Delta/P_{A,CO}} \]  

(1)

When KCO is multiplied by the volume of gas in the lung containing CO (alveolar volume (VA)), the total uptake of CO by the lung per unit of time per unit driving pressure is obtained. This product, \( K_{CO} \times V_{A} \), has been termed transfer factor of the lung for CO by the European community and diffusing capacity of the lung for CO (DLCO) by the North American community. The former term recognises that the measurement of CO uptake reflects a number of processes (not just diffusion), and is a submaximal value and, thus, not truly a "capacity". However, the latter term has considerable historical significance and, for the sake of uniformity, the ERS and ATS agreed to use the expression DLCO in this document.

The ERS recommends expressing DLCO in the SI units mmol·min⁻¹·kPa⁻¹, while the ATS prefers the traditional units mL (standard temperature, pressure and dry (STPD))·min⁻¹·mmHg⁻¹. In fact, this is not an important issue, providing the same set of units is used throughout all calculations. Values in SI units should be multiplied by 2.987 to obtain values in traditional units.

Determinants of CO uptake

The process of CO transfer from the environment to the pulmonary capillary blood includes: 1) bulk flow delivery of CO to the airways and alveolar spaces; 2) mixing and diffusion of CO in the alveolar ducts, air sacs and alveoli; 3) transfer of CO across the gaseous to liquid interface of the alveolar membrane; 4) mixing and diffusion of CO in the lung parenchyma and alveolar capillary plasma; 5) diffusion across the red cell membrane and within the interior of the red blood cell; and 6) chemical reaction with constituents of blood Hb [10–16].

The process of CO uptake can be simplified into two transfer or conductance properties: membrane conductivity (Dm), which reflects the diffusion properties of the alveolar capillary membrane; and the binding of CO and Hb. The latter can be represented as the product of the CO–Hb chemical reaction rate (h) and the volume of Hb in alveolar capillary blood (Vc).

Since these are conductances in series [14], these properties are related by:

\[ \frac{1}{DLCO} = \left(\frac{1}{Dm}\right) + \left(\frac{1}{h} \times V_c\right) \]  

(2)

A number of physiological changes can affect Dm or \( hV_c \) to influence DLCO. As the lung inflates, DM increases (due to unfolding membranes and increasing surface area), while \( V_c \) effects are variable (due to differential stretching and flattening of alveolar and extra-alveolar capillaries) [10, 17–24]. The net effect of these changes is that DLCO tends to increase as the lung inflates. Exercise, the supine position and Mueller manoeuvres (inspiratory efforts against a closed glottis) can all recruit and dilate alveolar capillaries, thereby increasing \( V_c \) and DLCO [25–31]. Alveolar-capillary recruitment also occurs in the remaining lung tissue following surgical resection, since the cardiac output now flows through a smaller capillary network. This causes a less than expected loss of \( V_c \) for the amount of lung tissue removed. In contrast, Valsalva manoeuvres (expiratory efforts against a closed glottis) can reduce \( V_c \) and thereby reduce DLCO [29].

The measurement of CO uptake is also affected by the distribution of ventilation with respect to DM or \( hV_c \) (i.e. CO uptake can only be measured in lung units into which CO was inspired and subsequently expired) [15, 16, 32, 33]. This is particularly important in diseases such as emphysema, where the inhaled CO may only go to the better-ventilated regions of the lung and the subsequently measured CO uptake will be determined primarily by uptake properties of those regions. Under these conditions, the tracer gas dilution used to calculate VA will also reflect primarily regional dilution and underestimate the lung volume as a whole. The resulting calculated DLCO should thus be considered to be primarily reflecting the gas-exchange properties of the ventilated regions of the lung.

In addition to these physiological and distributional effects on DLCO, a number of pathological states can affect DM, \( hV_c \), or both, and thereby affect DLCO (table 1) [5, 6, 34–43]. Measurement of DLCO is indicated when any of these pathological processes are suspected or need to be ruled out. Moreover, measuring changes in DLCO over time in these processes is a useful way of following the course of disease.
GAS ANALYSERS AND GENERAL EQUIPMENT

System design

Descriptions of the apparatus and general instructions for performing the single-breath diffusing capacity manoeuvre are available elsewhere [2, 44–48]. Equipment in clinical use varies widely in complexity, but the basic principles are the same. All systems have a source of test gas (bag-in-box, spirometer, compressed gas cylinder), a method for measuring inspired and expired volume over time (pirometers with kymographs, pneumotachometers near the mouthpiece or near a bag-in-box), and gas analysers (single-sample analysers or continuous high-speed analysers). Single-sample gas-analyser systems usually display only volume over time (fig. 1a). Continuous gas-analyser systems also provide a continuous tracing of CO and tracer gas concentrations during the test (fig. 1b).

Equipment requirements

Performance standards for equipment

The performance standards for equipment are as follows (table 2). 1) The volume-measurement accuracy should be the same as that established by the ATS/ERS for spirometry [49]; that is, ±3% volume accuracy (±3.5% accounting for 0.5% testing syringe error) over an 8-L volume range with test gases present in concentrations likely to be encountered during DLCO tests. Pneumotachometer devices for sensing flow and volume during the DLCO manoeuvre may be sensitive to different gas compositions, concentrations or pulsatile flow changes created by demand valves [50]. All devices should maintain the required volume accuracy, regardless of the gas mixture, direction of gas flow (e.g. inhaled or exhaled), or pulsatile flow pattern. 2) Gas-analyser accuracy is important in some circumstances, such as measuring CO "back pressure" (the expired fraction of CO when no CO has been inhaled). However, in calculating DLCO, only the ratios of alveolar to inhaled CO and tracer gas are needed. Thus, the analysers must primarily be able to produce an output for measured exhaled CO and tracer gas that is a linear extrapolation between the inhaled (test gas concentrations) and zero (no CO or tracer gas present in the analysers) [51, 52]. This is often referred to as a linear response. Since measured DLCO is very sensitive to errors in relative gas concentration, nonlinearity for the analysers should not exceed 0.5% of full scale (i.e. once the analysers have been adjusted to zero, with no test gas present and scaled to full scale using test gas concentrations, system nonlinearity on measurements of known dilutions of test gas should be no more than 0.5% of full scale). For example, if 0.300% CO is used for the test gas, then the maximum error on any dilution should be no more than ±0.0015%. 3) The gas analysers should have only minimal drift in zero and gain, so that output is stable over the test interval. Manufacturers are encouraged to provide a display of the measured gas concentrations so that stability can be confirmed. If significant

| TABLE 1 | Physiological and pathological changes that affect the carbon monoxide diffusing capacity of the lung (DLCO) |
|----------------------------------------------------------|
| **Extrapulmonary reduction in lung inflation (reduced Vₐ) producing changes in DM or Vc that reduce DLCO** |
| Reduced effort or respiratory muscle weakness |
| Thoracic deformity preventing full inflation |
| **Diseases that reduce Vc and thus reduce DLCO** |
| Anaemia |
| Pulmonary emboli |
| **Other conditions that reduce Vc and thus reduce DLCO** |
| Hb binding changes (e.g. HbCO, increased FO₂) |
| Valsalva manoeuvre (increased intrathoracic pressure) |
| **Diseases that reduce (in varying degrees) DM and Vc and thus reduce DLCO** |
| Lung resection (however, compensatory recruitment of Vc also exists) |
| Emphysema |
| Interstitial lung disease (e.g. IPF, sarcoidosis) |
| Pulmonary oedema |
| Pulmonary vasculitis |
| Pulmonary hypertension |
| **Diseases that increase Vc and thus increase DLCO** |
| Polycythaemia |
| Left-to-right shunt |
| Pulmonary haemorrhage (not strictly an increase in Vc, but effectively an increase in lung Hb) |
| Asthma |
| **Other conditions that increase Vc and thus increase DLCO** |
| Hb binding changes (e.g. reduced FO₂) |
| Muller manoeuvre (decreased intrathoracic pressure as in asthma, resistance breathing) |
| Exercise (in addition, a possible DM component) |
| Supine position (in addition, possibly a slight increase in DM) |
| Obesity (in addition, a possible DM component) |

Vc: alveolar volume; DM: membrane conductivity; FO₂: carbon monoxide (CO)–haemoglobin (Hb) chemical reaction rate; Vc: volume of pulmonary capillary blood; FO₂: inspired fraction of oxygen; IPF: idiopathic pulmonary fibrosis; Hb: haemoglobin.
drift is present over the time scale of a test (~30 s), then adjustment algorithms should be devised to compensate for the analyser drift from measured data. Gas-analyser stability should be ±0.001% absolute for CO and ±0.5% of the full-scale reading for the tracer gas. 4) If CO₂ and/or H₂O interfere with gas-analyser performance, there are two remedies. First, the CO₂ and/or H₂O can be removed from the test gases before passage through the gas analysers. H₂O is commonly absorbed by anhydrous CaSO₄ or by other products. Absorption of CO₂ can be achieved with either Ba(OH)₂ or NaOH. Both generate H₂O when combining with CO₂. Therefore, if a CO₂ absorber is used, it must precede the H₂O absorber in the gas-analyser circuit. Selectively permeable tubing can also be used to remove water vapour; however, this tubing may only reduce the water vapour to near ambient levels, and remaining H₂O can still interfere with the gas-analyser performance. Furthermore, water vapour-permeable tubing has a limited life expectancy. One method of checking water vapour-permeable tubing is to compare gas-concentration measurements made with both dry and humidified test gas, and make adjustments described as follows. Manufacturers should provide a replacement schedule for water vapour-permeable tubing and/or a method for checking its function. The second remedy for CO₂ and/or H₂O analyser interference is to characterise the effect of these gases on analyser output, and then adjust the output of the analysers for the presence of the interfering gas species. Two approaches are often employed as follows: assume constant concentrations of the interfering gases and apply a fixed correction factor across all tests; or directly measure the CO₂ and/or H₂O for each test and make proportional adjustments in the analyser output based on the measured concentrations for CO₂ and/or H₂O (see CO₂, H₂O and temperature adjustment for VA calculations section). 5) Circuit resistance should be <1.5 cmH₂O·L⁻¹·s⁻¹ at 6 L·s⁻¹ flow. If a demand-flow regulator is used on a compressed test gas cylinder, the maximal inspiratory pressure required for 6 L·s⁻¹ inspiratory flow through both circuit and valve should be <10 cmH₂O. 6) The timing device in the DLCO apparatus should be accurate to within 1% (100 ms over 10 s). The timing technique used for calculation should be identified. If an instrument provides automatic data computation, the accuracy of breath-hold time computation should be documented. 7) Dead space volume (Vd) for both inspired test gas and the alveolar sample should be known, and their role in all data-computation algorithms identified and documented. For adults, the Vd of the valve, filter and mouthpiece should total <0.350 L. Smaller Vd volumes may be needed for paediatric applications. 8) The system must be leak free. This is particularly important for DLCO systems that aspirate gas samples at subatmospheric pressure through the gas analysers. When samples are aspirated, leaks in tubing, fittings and other locations allow room air to be drawn into the gas circuit, diluting the sample and reducing the concentrations of test gases.

Equipment quality control
The considerations for equipment quality control are as follows (table 3). 1) Prior to each test, gas analysers should be zeroed. After each test, a new zeroing procedure should be carried out to account for analyser drift during the test. 2) Each day, there should be a volume calibration with a 3-L syringe [53]. Technicians should also note significant discrepancies between inspired volume (VI) and vital capacity (VC), or VA and total lung capacity (TLC) that might suggest volume-calibration

### Table 2: Equipment specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume accuracy</td>
<td>ATS/ERS standards (currently 3.5% accuracy over an 8-L volume using test gases, with a testing syringe accuracy of 0.5%)</td>
</tr>
<tr>
<td>Gas analysers</td>
<td>Linear from zero to full span within ±0.5% of full span. Stable over the duration of the test with drift &lt;±0.5% of a measured gas</td>
</tr>
<tr>
<td>Circuit resistance</td>
<td>&lt;1.5 cmH₂O·L⁻¹·s⁻¹ at a flow of 6 L·s⁻¹</td>
</tr>
<tr>
<td>Demand-valve sensitivity</td>
<td>&lt;10 cm H₂O required for 6 L·s⁻¹ flow through valve and circuit (if compressed gas source used)</td>
</tr>
<tr>
<td>Timer</td>
<td>±1.0% over 10 s (100 ms)</td>
</tr>
<tr>
<td>Apparatus/valve filter V₀</td>
<td>&lt;0.350 L</td>
</tr>
</tbody>
</table>

problems. 3) Each week, or whenever problems are suspected, the following procedures should be carried out. First, leak testing should be done if it is appropriate to the instrument being used. Secondly, a DL,CO test with a calibrated 3.0-L syringe should be used, which is performed by attaching the syringe to the instrument in the test mode. Test gas is withdrawn from the DL,CO machine by the syringe and then reinserted at the end of the breath-hold. The measured DL,CO should be near zero and the measured VI should be ~3.3L (3.0 L x the body temperature, ambient pressure, saturated with water vapour (BTPS) factor). This procedure checks the inhaled volume accuracy in the DL,CO test mode, which may be in error when spirometry measurements are not. Thirdly, a test could be performed on a “standard subject” (biological control) or simulator [54]. Standard subjects are healthy nonsmokers (e.g. healthy laboratory personnel). If the DL,CO in a standard subject varies >10% from known previous values, the test should be repeated. If the repeat test confirms the finding, the DL,CO system should be evaluated carefully for the possibility of leaks, nonlinear analyser function, volume and time inaccuracy, etc. When sufficient data on a standard individual are obtained, laboratories should establish their own outlier criteria to serve as indicators of potential problems with their DL,CO systems. Manufacturers are encouraged to develop automated quality-control systems to assist and enhance the utility of these steps. 4) Gas-analyser linearity should be assessed every 3 months. A straightforward approach is to measure known serial dilutions of the test gas [55], or measure the concentration of a separate high-precision test gas having a certificate of analysis. At least one intermediate concentration should be used to check linearity. Manufacturers should be encouraged to automate this function. In addition, the timer should be assessed for accuracy every quarter. 5) Records of equipment checks and standard subject tests should be dated, signed and kept in a laboratory log book. Manufacturers are encouraged to provide software and test equipment options for quality-control measurements and quality-control data management.

**Infection control**

The major goal of infection control is to prevent the transmission of infection to patients and staff during pulmonary function testing. The recommendations in the ATS/ERS documents for spirometry and general considerations for pulmonary function testing also apply to DL,CO equipment and procedures [49, 56].

**SINGLE-BREATH TESTING TECHNIQUE STANDARDISATION ISSUES**

The single-breath determination of DL,CO involves measuring the uptake of CO from the lung over a breath-holding period.

To minimise variability as much as possible, the following recommendations for the standardisation of testing techniques are offered.

**Patient conditions for measurement**

Factors that affect VC (e.g. exercise, body position, and Hb affinity for CO, such as alveolar oxygen partial pressure \(P_{A,O_2}\), and carboxyhaemoglobin (COHb)) should be standardised. If clinically acceptable, the subject should not breathe supplemental oxygen for 10 min prior to a standard test. When using exercise or the supine position to assess the “recruitability” of DL,CO [15, 25–28], the level of exercise and/or the duration of the supine position should be noted.

Before beginning the test, the manoeuvres should be demonstrated and the subject carefully instructed. The subject should be seated comfortably throughout the test procedure. The test should be performed at a stable comfortable temperature within manufacturer’s equipment specifications.

COHb produces an acute and reversible decrease in DL,CO [57–60], largely due to the effects on CO back pressure and the “anaemia effect” from decreased Hb binding sites for CO from the test gas. As cigarette smoking is the most common source of COHb, subjects should be asked to refrain from smoking or other CO exposures on the day of the test. The time of the last cigarette smoked should be recorded and noted for the interpretation. A correction for CO back pressure should be made for recent or heavy cigarette smoking (see Adjustment for carboxyhaemoglobin concentration and CO back pressure section). Manufacturers are encouraged to provide the capability to do this easily.

**Inspiratory manoeuvre**

Once the mouthpiece and nose clip are in place, tidal breathing should be carried out for a sufficient time to assure that the subject is comfortable with the mouthpiece. Deep inspirations should be avoided during this period as they can increase subsequent CO uptake [61]. The DL,CO manoeuvre begins with unforced exhalation to residual volume (RV). In obstructive lung disease, where exhalation to RV may require a prolonged period, a reasonable recommendation is that this portion of the manoeuvre should be limited to 6 s, a time consistent with using the forced expiratory volume in six seconds manoeuvre as a surrogate for VC [49]. At RV, the subject’s mouthpiece is connected to a source of test gas, and the subject inhales rapidly to TLC.

A submaximal inspired volume (i.e. less than the known VC) can affect CO uptake, depending upon whether it is a result of an initial suboptimal exhalation to RV (test performed at TLC) or whether it is due to a suboptimal inhalation from RV (test performed below TLC) [19–22]. In the former case, the calculated VA and DL,CO will accurately reflect lung volume and the CO uptake properties of the lung at TLC. In the latter case, the VA will be reduced and DL,CO measurement will be affected (see Adjustment for lung volume section).

Due to these effects, it is important that the VI be as close to the known VC as possible. Data from a large patient population have shown that the VI during DL,CO measurements averages ~90% of the VC [19], but that as many as 32% of subjects may

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**TABLE 3** Equipment quality control

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas-analyser zeroing</td>
<td>Done before/after each test</td>
</tr>
<tr>
<td>Volume accuracy</td>
<td>Tested daily</td>
</tr>
<tr>
<td>Standard subject or simulator testing</td>
<td>Tested at least weekly</td>
</tr>
<tr>
<td>Gas-analyser linearity</td>
<td>Tested every 3 months</td>
</tr>
<tr>
<td>Timer</td>
<td>Tested every 3 months</td>
</tr>
</tbody>
</table>


fall below this target \[62\]. A more recent study of >6,000 DLCO measurements in a university laboratory demonstrated that 72, 86 and 92% of these patients could achieve \( V_l \) targets of 90, 85 and 80%, respectively, of the known VC \[63\]. Since it appears that \( V_l \) reductions of as much as 15% of the known VC will reduce the DLCO <5% \[19\], a \( V_l \) target of 85% of the largest-known VC seems both reasonable and attainable.

The inspiration should be rapid, since the DLCO calculations assume ‘instantaneous’ lung filling \[24, 64–70\]. Slower lung filling decreases the amount of time the lung is at full inspiration with a consequent reduction in CO uptake. Although various sample timing techniques address the issue of lung filling and emptying time, it is still reasonable to expect that 85% of \( V_l \) should be inspired in <4.0 s. If longer inspiratory times are needed to achieve the 85% \( V_l \) goal, this should be noted on the test report.

**Condition of the breath-hold and expiratory manoeuvre**

Valsalva (inspiratory efforts against a closed airway) and Muller manoeuvres (inspiratory efforts against a closed airway) during the breath-hold, by decreasing and increasing thoracic blood volume, respectively, will decrease and increase DLCO, respectively \[29, 71, 72\]. The intrapulmonary pressure during the breath hold should thus be near atmospheric, and this is best accomplished by having the subject voluntarily maintain full inspiration using only the minimal effort necessary. The breath-hold time should be 10 ± 2 s, a target easily achieved in the vast majority of subjects \[62\].

As with inspiration, the DLCO calculation assumes instantaneous lung emptying \[24, 64–69\]. Although various sample timing techniques address the fact that emptying is not instantaneous, it is still reasonable to expect that the expiratory manoeuvre should be smooth, unforced, without hesitation or interruption, and total exhalation time should not exceed 4 s (with sample collection time <3 s). In subjects who require a longer expiratory time to provide an appropriate alveolar gas sample, the expiratory time should be noted in the test report. Common errors that can occur during the inspiration, breath-hold and expiration manoeuvres are given in figure 2.

**Washout and sample collection volume**

The DLCO calculations (see Calculations section) require alveolar gas samples. During expiration, a volume of gas must be expired and discarded to clear anatomic and mechanical \( V_D \) before the alveolar sample is collected (fig. 1). Contamination of the alveolar gas sample with \( V_D \) gas will cause an underestimation of true CO uptake. In general, the washout volume should be 0.75–1.0 L (BTPS). If the patient’s VC is <2.00 L, the washout volume may be reduced to 0.50 L. Newer devices can provide a graphical display of exhaled gas concentrations to assure that \( V_D \) gas is not present in the alveolar sample (fig. 1). Using such an analyser, HuAng et al. \[71\] showed that the standard approach noted above adequately cleared \( V_D \) in >90% of adults.

The sample gas volume (\( V_S \)) is the volume of gas used to analyse alveolar CO and tracer gas concentrations at the end of the breath-hold. In subjects with good gas mixing and uniform ventilation and CO uptake properties, virtually any gas sample after \( V_D \) washout will be a good reflection of the lung as a whole. However, in subjects with poor gas mixing or marked sequential emptying of various lung regions, the gas sample collected will only reflect the properties of the regions contributing to that sample. \( V_S \) collection time will also affect the measurement of breath-hold time (see below). In order to standardise the collection process, a \( V_S \) of 0.50–1.00 L should be collected for analysis. In patients with VC <1 L, a \( V_S \) <0.50L may be used if it can be assured that the \( V_D \) has been cleared.

If continuous analysers with graphical displays are used, computerised or visual inspection of the expired CO and tracer gas curves may be used to adjust washout and the \( V_S \) if needed (fig. 1) \[71\]. These adjustments may be useful in subjects with VC <1 L who are unable to meet the minimum \( V_D \) washout and \( V_S \) recommended previously (e.g. paediatric patients, or adult patients with severe restrictive processes). These adjustments may also be useful in subjects with a large \( V_D \) in whom the recommended value range of 0.75–1.0 L is inadequate. For these adjustments to be achieved properly, the displays must represent actual gas concentrations that occurred at the mouth, synchronised for delays in gas transport and adjusted for gas-analyser response. In making such adjustments, the start of the \( V_S \) (end of the washout) must clearly be at a point where the tracer gas has started to plateau after the immediate fall from its inspiratory concentration, and the CO curve has ceased its immediate fall and started a smooth gradual decline (fig. 1). Furthermore, reports must indicate that manual adjustments were used to select washout volumes and \( V_S \), so the interpreter can review and verify the adjustments.

**Inspired gas composition**

The test gases used to calculate DLCO include a tracer gas to measure \( V_A \), as well as CO. The remainder of the test gas mixture includes \( O_2 \) and \( N_2 \).

The tracer gas should be relatively insoluble and chemically and biologically inert. Since the tracer gas is used to determine the initial alveolar CO concentration, as well as the \( V_A \) from
which CO uptake is occurring, its gaseous diffusivity should be similar to CO. It should not interfere with the measurement of CO concentration. The tracer gas should not ordinarily be present in alveolar gas or else be present at a known, fixed concentration (e.g. argon).

Commonly used tracer gases are helium (He) and methane (CH₄). While He meets most of the previous criteria, its gaseous diffusivity is considerably higher than CO. CH₄ is commonly used as a tracer gas for systems that continuously sample expired gas. Its gaseous diffusivity is closer to CO, but it has a slightly higher liquid solubility than He. As new tracer gases are introduced, manufacturers should demonstrate that they produce VA and DL,CO values equivalent to those measured using He, as this is the tracer gas that is used to derive most of the available reference equations.

The inspired CO should nominally be 0.3%. However, as ratios are more important than absolute values, exact concentrations are not critical. The assumption in calculating CO uptake is that capillary blood does not contain CO. Thus, corrections are needed in patients who have significant COHb (see Adjustment for COHb concentration and CO back pressure section).

Since PAO₂ fluctuates over the ventilatory cycle [72] and can affect CO uptake by affecting 0, a more stable PAO₂ during the DL,CO manoeuvre would seem desirable and, theoretically, can be achieved with a test gas fraction of inspired oxygen (FI,O₂) of 0.17. Most current systems use either a FI,O₂ of 0.21 (with fractional concentrations of tracer gases such as CH₄ of <0.01), or gas mixtures containing CO and 10% He with “balance air” (an effective FI,O₂ of 0.19). Since DL,CO will increase 0.31 to 0.35% for each 0.133 kPa (1 mmHg) drop in PAO₂ [73, 74], the increase in DL,CO that would be expected as the FI,O₂ is decreased from 0.21 to 0.17 (PAO₂ decreased ~3.7 kPa (~28 mmHg)) is 8–9%. It is recommended that laboratories use gas mixtures with inspired oxygen partial pressure (PFI,O₂) values similar to the reference set used in the interpretation (table 4) [75–82], or make appropriate adjustments of measured or predicted DL,CO for the PFI,O₂.

By measuring DL,CO at several different levels of PAO₂, the two components of DL,CO (DM and Vₐ) can be distinguished. This is accomplished by using the Roughton–Forster relationship noted previously (equation 2) and varying θ (the reaction rate of O₂ and Hb) by altering the PFI,O₂. Subsequently, 1/DL,CO is plotted against 1/0 at the different PFI,O₂ levels. The slope of this relationship is 1/Vₐ and the intercept is 1/DM.

**Interval between tests**

At least 4 min should be allowed between tests to allow an adequate elimination of test gas from the lungs. The subject should remain seated during this interval. In patients with obstructive airway disease, a longer period (e.g. 10 min) should be considered. Several deep inspirations during this period may help to clear test gases more effectively. If continuous monitoring of expired gas concentrations is available, the washout of tracer gas from the previous test may be confirmed by observing end-tidal gas concentrations before beginning the next test.

**Miscellaneous factors**

There may be diurnal variation in DL,CO, since one study has found that DL,CO fell 1.2–2.2% per hour throughout the day [83]. The reason for the change was not clear and was not explained by CO back pressure or changes in VA, Vₐl or breath-hold time. One explanation is a combination of changes in CO back pressure and diurnal variation in Hb concentration [84]. A 13% change in DL,CO during the menstrual cycle has been reported [85]. The highest value was observed just before the menses, and the lowest was on the third day of menses. It is not clear, however, if this is simply a Hb effect or whether it reflects other physiological processes (e.g. hormonal changes on pulmonary vascular tone). Ingestion of ethanol has been reported to decrease DL,CO [86]. The mechanisms involved are not clear, although it is known that some fuel-cell CO analysers are sensitive to exhaled ethanol and ketones. In obstructive lung disease subjects, after administration of a bronchodilator, DL,CO may increase up to 6% [87]. Bronchodilators can affect VA, vasomotor tone, etc., and their use prior to testing could conceivably optimise these factors. Use of a bronchodilator should be noted in the interpretation [88].

**TABLE 4**

Inspirited gas mixtures used during measurements of normal carbon monoxide (CO) uptake for commonly used reference equations

<table>
<thead>
<tr>
<th>Author [Ref.]</th>
<th>Gas mixture*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TECULESCU [75]</td>
<td>1.5% He, balance air (FI,O₂ 0.20)</td>
</tr>
<tr>
<td>VAN GANSE [76]</td>
<td>14–15% He, balance air (FI,O₂ 0.18)</td>
</tr>
<tr>
<td>FRANS [77]</td>
<td>10% He, 18% O₂</td>
</tr>
<tr>
<td>CRAPO [78]</td>
<td>10% He, 25% O₂ (comparable to 21% at sea level)</td>
</tr>
<tr>
<td>PAOLETTI [79]</td>
<td>10% He, 20% O₂</td>
</tr>
<tr>
<td>KNUDSON [80]</td>
<td>10% He, 21% O₂</td>
</tr>
<tr>
<td>ROCA [81]</td>
<td>13% He, 18% O₂</td>
</tr>
<tr>
<td>HUANG [25]</td>
<td>0.3% CH₄, 0.3% C₂H₂, balance air (FI,O₂ 0.20)</td>
</tr>
<tr>
<td>MILLER [82]</td>
<td>10% He, ?balance air</td>
</tr>
</tbody>
</table>

He: helium; FI,O₂: inspired oxygen fraction; CH₄: methane; C₂H₂: acetylene. *: in addition to 0.3% CO.

**CALCULATIONS**

The transfer factor or diffusing capacity for a gas in the lungs (DL) equals its rate of exchange across the lung divided by its transfer gradient:

\[ DL = \text{rate of gas uptake/transfer pressure gradient} \] (3)

The rate of gas uptake is expressed in mL STPD·min⁻¹, and the transfer gradient (the difference between alveolar and pulmonary capillary pressures) in mmHg. Thus, DL,CO has traditional units of mL STPD·min⁻¹·mmHg⁻¹ (SI units of mmol·min⁻¹·kPa⁻¹). For CO, the pulmonary capillary CO tension is near zero and thus:

\[ DL,CO = \frac{\Delta \text{CO uptake over time}}{P_{A,CO}} \]

\[ = \frac{\Delta \text{CO}}{V_{A}}/\Delta P_{A,CO} \] (4)

The single-breath DL,CO technique assumes that both CO and the tracer gas (Tr) are diluted comparably on inspiration. Thus,
the initial alveolar partial pressure of CO \((P_{A,CO,0})\) can be calculated by knowing the inspired tracer gas fraction \((F_{I,Tr})\) and fraction alveolar tracer gas \((F_{A,Tr})\):

\[
F_{A,CO,0} = F_{I,CO} \times F_{A,Tr}/F_{I,Tr}
\]

\[(5)\]

\[
P_{A,CO,0} = P_b \times F_{A,CO,0}
\]

\[(6)\]

where \(F_{A,CO,0}\) is the initial alveolar inspired CO fraction, \(F_{I,CO}\) is the inspired CO fraction, \(P_b\) is the barometric pressure and \(F_{A,CO,0}\) is the initial alveolar CO fraction.

Tracer gas dilution is also used to determine the effective \(V_A\) as described below. Solving for \(D_{L,CO}\) thus yields the equation:

\[
D_{L,CO} = \frac{(V_A/\langle t/60 \times (P_b - P_{H_2O})\rangle) \times \ln((F_{I,Tr} \times F_{I,CO})/ (F_{I,Tr} \times F_{A,CO}))}{(7)\}

where \(V_A\) is in mL STPD, \(t\) is breath-hold time in seconds, and \(P_{H_2O}\) is water vapour pressure.

**Calculating breath-hold time**

The “breath-hold time” or time of transfer during which CO changes from its initial to final concentration is in the denominator of the \(D_{L,CO}\) equation (equation 7). As noted previously, the single-breath measurement of CO uptake assumes an “instantaneous” lung filling and emptying process. However, both inspiration and expiration require up to several seconds, and these periods of changing gas volume in the lung must be accounted for in the calculations. For purposes of standardisation, the method by Jones and Meade [68] (fig. 3) is recommended, since it has the theoretical appeal of empirically accounting for the effects of inspiratory and expiratory time. This method has also been shown to adequately address inspiratory flows as low as 1 L.s\(^{-1}\), breath-hold times as short as 5 s, and expiratory flows as low as 0.5 L.s\(^{-1}\) in normal subjects [64].

With the approach taken by Jones and Meade [68], breath-hold time equals the time starting from 0.3 of the inspiratory time to the middle of the sample collection time. As in spirometry, the back-extrapolation technique should be used to establish time zero [48, 49]. The time when 90% of the \(V_I\) has been inspired is a reasonable end point for defining inspiratory time (fig. 3).

A theoretically more accurate way to account for volume changes over time during inspiration and expiration is to use three separate equations for \(D_{L,CO}\) during inspiration, breath hold and expiration (the “three-equation” technique) [24, 64]. This algorithm is commercially available and may be particularly useful in subjects unable to rapidly fill or empty their lungs. However, clinical experience with this approach is limited.

Other breath-hold timing algorithms may be appropriate in maintaining consistency (e.g. longitudinal studies), but these measurements should be recognised as less suitable recommendations.

**Calculating the alveolar volume**

\(V_A\) represents an estimate of lung gas volume into which CO is distributed and then transferred across the alveolar capillary membrane [3, 4]. Thus, it is critical in the measurement of \(D_{L,CO}\). As noted previously, \(V_A\) is measured simultaneously with CO uptake by calculating the dilution of an inert Tr. For normal subjects, this calculated single-breath determination of \(V_A\) \((V_{A,mb})\) plus estimated \(V_D\) closely matches TLC determined by plethysmography [19, 70]. However, poor gas mixing in patients with maldistribution of inspired volume (e.g. obstructed airways patients) can markedly reduce Tr dilution and, thus, lead to values for \(V_{A,mb}\) that are markedly less than a \(V_A\) determined from the actual total thoracic gas volume \((V_TG)\). The observed CO uptake is also affected by poor gas mixing under these conditions, and will primarily reflect the CO transfer properties of the regions into which the test gas is distributed. It has been suggested that a separately determined \(V_A\) from a more accurate technique (e.g. multiple-breath technique \((V_{A,mb})\) or plethysmography \((V_{A,plethys})\)) could be substituted for \(V_{A,mb}\) under these conditions to “correct” for the effects of maldistribution. However, the \(D_{L,CO}\) calculation (equations 4 and 7) is based on the volume of gas into which the Tr (and CO) distributes, and not the total \(V_TG\). Moreover, substituting a larger, separately determined \(V_{A,mb}\) or \(V_{A,plethys}\) assumes that \(D_M\) and \(V_c\) properties in the unmeasured lung regions are similar to those in the measured lung regions, an assumption that is difficult to justify. Due to these considerations, a separately measured \(V_{A,mb}\) or \(V_{A,plethys}\) should not be substituted for \(V_{A,mb}\). Instead, when the \(V_{A,mb}\) is markedly less than a separately determined \(V_{A,mb}\) or \(V_{A,plethys}\), this should be reported and the ratio of \(V_{A,mb}\) to \(V_{A,mb}\) or \(V_{A,plethys}\) reported. For the subsequent interpretation of \(D_{L,CO}\), it should then be noted that the maldistribution of inspired gas probably contributed to any observed reduction in measured \(D_{L,CO}\).
The volume of distribution for the tracer gas can be determined from values for \( V_I, F_{I,Tr} \) and \( F_{A,Tr} \), and knowing the conditions of the inspired and expired gases. Since the amount of tracer gas in the lung (alveolar plus dead space) equals the amount of inspired tracer gas, and the dead space tracer gas fraction is the same as the inspired fraction (all expressed at BTPS):

\[
V_I \times F_{I,Tr} = V_A \times F_{A,Tr} + V_D \times F_{I,Tr}
\]  
(8)

\[
V_A = V_I - V_D \times (F_{I,Tr}/F_{A,Tr})
\]  
(9)

Although \( V_A \) is usually expressed under BTPS conditions, it must be converted to STPD conditions to calculate \( DL_{CO} \) in equation 7.

It is essential that \( V_D \) is considered in the calculation of \( V_A \). \( V_D \) occurs in two areas: instrument \( V_D \) (i.e. volume of the mouthpiece, filters and connections within the valving system); and anatomic \( V_D \) (i.e. the volume in the conducting airways that does not participate in gas exchange). Instrument \( V_D \) should be specified by the manufacturer, but may vary as the user alters the system (e.g. addition of a filter).

There are various methods to estimate anatomic \( V_D \). Examples include a fixed value of 150 mL [1] (although this does not work well for small adults or children), and another of 2.2 mL x kg body weight [47] (although this does not work well for very obese subjects). In studies deriving the commonly used reference equations (table 4), the most commonly used technique was to assume 2.2 mL x kg body weight. However, some investigators ignored anatomic \( V_D \) [79, 80, 82], and one used age+2.2mL x kg body weight [78]. If the body mass index is <30, the current authors recommend using an estimate for anatomic \( V_D \) of 2.2 mL x kg body weight. In more obese subjects or if the weight is unknown, \( V_D \) (mL) can be estimated using the following equation:

\[
V_D = 24 \times \text{height} \times \text{height}/4545
\]  
(10)

where height is measured in cm, or:

\[
V_D = 24 \times \text{height} \times \text{height}/703
\]  
(11)

where height is measured in inches.

In single-sample systems, the sample-bag residual volume (sometimes called a sample-bag dead space) dilutes the sample gas and alters the measured concentrations of expired gases. The size and direction of the error depends on \( V_S \), the residual volume of the sample bag and its connectors (\( V_{SRV} \)), and \( V_{SRV} \) gas content. \( V_{SRV} \) could contain test gas, room air or expired gas from a subject (after a \( DL_{CO} \) test). When \( V_{SRV} \) contains room air, its effect is to reduce the measured concentrations of expired gases. The following equation adjusts for this:

\[
\text{Adjusted } F_{A,Tr} = \frac{\text{measured } F_{A,Tr}}{V_S/(V_S - V_{SRV})}
\]  
(12)

Estimates of the potential change in \( DL_{CO} \) in existing systems when no adjustment is made for sample-bag dead space range from 0.3–8%, depending on sample-bag size and \( V_{SRV} \) [89].

Manufacturers should report instrument and sample-bag dead space. Both of these must be flushed with room air (or, if \( DM \) and \( V_c \) are to be calculated, appropriate levels of oxygen) before the single-breath manoeuvre so that it will not contain expiratory gas from a previous subject. \( V_{SRV} \) should be <2% of the \( V_S \) or 10 mL, whichever is larger.

**Inspired gas conditions**

Though inspired gas is often assumed to be measured at ambient temperature and pressure, saturated with water vapour conditions, this is only true in systems in which the test gas is transferred to a water-sealed spirometer before it is inspired. In most cases, the test gas inspired from a bag-in-box system, through a pneumotachometer from a bag, or a compressed gas cylinder with a demand valve is a dry gas (<10 ppm H\(_2\)O) and, thus, at ambient temperature and pressure, dry conditions. The inspired volume needs to be converted to BTPS conditions to use in equations 7, 8 and 9. It is recommended the \( V_I \) (BTPS) be reported, and manufacturers should specify and document inspired gas conditions for each instrument.

**\( CO_2 \), \( H_2O \) and temperature adjustment for \( V_A \) calculations**

Exhaled gas contains \( CO_2 \) and \( H_2O \), which were not present in the test gas mixture. As noted previously, some systems remove one or both of these if they interfere with analyser function, and this will raise both \( CO \) and tracer gas concentrations. Under these circumstances, adjustments are required for the increase in \( F_{A,Tr} \) to calculate \( V_A \) (table 5). However, no adjustment for the increase in alveolar inspired \( CO \) fraction at time \( t \) (\( F_{A,CO,t} \)) and \( F_{A,Tr} \) is necessary in calculating the rate of \( CO \) uptake, since the concentration factor appears in both the numerator and the denominator of the expression (\( F_{A,CO,t}/F_{A,CO} \)) and therefore cancels.

Exhaled gas is initially at body temperature. Some systems allow this to cool (gas volume contracts), whereas others will provide heat to maintain the temperature. Adjustments to BTPS conditions may be required depending upon the system design (table 5).

All of these adjustments should be documented by the manufacturer for their particular system.

**EVALUATING THE MEASUREMENT OF \( DL_{CO} \)**

**Acceptability, repeatability and number of tests**

Acceptable tests are defined in table 6. Repeatability describes the variability on repeated testing with no change in test conditions [90, 91]. In a large university-based laboratory study, a coefficient of variation of repeated measurements in normal subjects was 3.1%, and this increased only slightly (from 4.0 to 4.4%) in patients with abnormal spirometry patterns [63]. In contrast, an inter-session \( DL_{CO} \) variability of up to 9% (reproducibility) has been documented in normal individuals in repeated measurements over a period of 1 yr [92].

Since most intra-session variability is technical rather than physiological, the mean of acceptable tests is reasonable to report. In this report, there should be at least two acceptable tests that meet the repeatability requirement of either being within 3 mL CO (STPD)-min\(^{-1}\)-mmHg\(^{-1}\) (or 1 mmol-min\(^{-1}\)-kPa\(^{-1}\)) of each other or within 10% of the highest value. In a large university-based laboratory study, >95% of the patients could meet this criteria [63].
The average of at least two acceptable tests that meet this repeatability requirement should be reported (i.e. outliers excluded). While it is recommended that at least two DL\textsubscript{CO} tests should be performed, research is needed to determine the actual number of tests required to provide a reasonable estimate of average DL\textsubscript{CO} value for a given person. As noted below, five tests will increase COHb by ~3.5% [84], which will decrease the measured DL\textsubscript{CO} by ~3-3.5%. Thus, more than five tests are not recommended at the present time.

**Adjustments to the measurement of DL\textsubscript{CO} prior to interpretation**

DL\textsubscript{CO} depends upon a number of physiological factors. Besides varying with age, sex, height and possibly race, DL\textsubscript{CO} also changes with Hb, lung volume, COHb, P\textsubscript{O}\textsubscript{2} (e.g. altitude), exercise and body position. Although these effects may cause changes in DL\textsubscript{CO} in opposite directions [93], all should be considered in interpreting the observed CO uptake. Moreover, specific adjustments for three of these factors (Hb, COHb and P\textsubscript{O}\textsubscript{2}) should always be made to ensure appropriate interpretation (see below). Consideration could also be given to adjust for a submaximal inspiration resulting in a less than expected VA.

**Adjustment for haemoglobin**

Since CO–Hb binding is such an important factor in CO transfer, DL\textsubscript{CO} changes can be substantial as a function of Hb concentration [93–97]. The empirical change in DL\textsubscript{CO} with Hb change closely matches what is expected from a theoretical approach using the relationship in equation 2, with \( t \) assumed to be proportional to the Hb, DM/\( 0\text{Vc} \) is assumed to be 0.7 [96], and the “standard” Hb value is assumed to be 14.6 g dL\textsuperscript{−1} (9 mmol l\textsuperscript{−1}) SI in adult males and adolescents and 13.4 g dL\textsuperscript{−1} (8.26 mmol l\textsuperscript{−1}) SI in adult females and children <15 yrs. Using these relationships and expressing Hb in g dL\textsuperscript{−1}, the equation for adjusting predicted DL\textsubscript{CO} in adolescents and adult males is:

\[
\text{DL}_{\text{CO, predicted}} = \frac{(1.7 \text{ Hb}/(10.22 + \text{Hb}))}{\text{DL}_{\text{CO, predicted}}} 
\]

The equation for adjusting predicted DL\textsubscript{CO} in children <15 yrs of age and females is:

\[
\text{DL}_{\text{CO, predicted}} = \frac{(1.7 \text{ Hb}/(9.38 + \text{Hb}))}{\text{DL}_{\text{CO, predicted}}} 
\]

Results from a more recent study in patients with a wide range of Hb abnormalities [97] showed a slightly greater and more
linear relationship, but corrected values were generally consistent with equations 13 and 14.

Adjustments for $P_{A,O_2}$

As noted previously, $P_{A,O_2}$ affects the measurement of $Dl,CO$. $P_{A,O_2}$ changes will occur as a consequence of supplemental O$_2$ breathing (higher $P_{A,O_2}$) or performing $Dl,CO$ assessments at altitude (lower $P_{A,O_2}$). As mentioned before, $Dl,CO$ will change by ~0.35% per mmHg change in $P_{A,O_2}$ [73, 74] or by ~0.31% per mmHg decrease in $P_{I,O_2}$. Adjustments to the predicted $Dl,CO$ in a subject on supplemental O$_2$ may be made using a measured $P_{A,O_2}$ and assuming a normal $P_{A,O_2}$ on room air at a sea level of 100 mm Hg, as follows:

$$Dl,CO,\text{predicted for elevated }P_{A,O_2} = Dl,CO,\text{predicted}/(1.0 + 0.0035(P_{A,O_2} - 100))$$ (15)

If the adjustment is being made for altitude, assuming a $P_{I,O_2}$ of 150 mmHg at sea level:

$$Dl,CO,\text{predicted for altitude} = Dl,CO,\text{predicted}/(1.0 + 0.0031(P_{I,O_2} - 150))$$ (16)

Adjustment for COHb concentration and CO back pressure

COHb can affect the measured uptake in the following two ways [98–100]. First, by occupying Hb binding sites, CO produces an “anaemia effect”. Secondly, CO partial pressure in the blood will reduce the driving pressure for CO transport from alveolar gas to capillary blood.

Exposure to ordinary environmental CO and endogenous production of CO as a byproduct of Hb catalysis commonly results in measured COHb levels of 1–2% [98]. The 1–2% baseline COHb levels that are attributable to endogenous production of CO and ordinary environmental exposures are already incorporated into reference values based on healthy nonsmoking subjects. Cigarette smoke and other environmental sources, however, can produce measurable levels of CO back pressure and COHb that may need to be considered in the measurement of CO uptake [99]. Small increases in COHb also occur when CO is inspired in the $Dl,CO$ test. FRY et al. [84], for example, found that COHb increased by ~0.7% with each single-breath $Dl,CO$ test.

CO back pressure can be measured in expired gas before a $Dl,CO$ manoeuvre or estimated using one of several available techniques [100–103]. For example, CO back pressure can be calculated from COHb from the following equation:

$$\text{alveolar }[CO] = (\text{COHb/O}_2\text{Hb}) \times (\text{alveolar }[O_2])/210$$ (17)

$Dl,CO$ can then be recalculated after subtracting the estimated CO back pressure from both the initial and final alveolar CO. Units must be consistent before making the subtraction. However, this method will not adjust $Dl,CO$ for the “anaemia” effect of COHb.

Several studies have evaluated both the empirical and theoretical effects of COHb on $Dl,CO$ and incorporated both the back pressure and the “anaemia” effects of COHb. In general, a 1% increase in COHb reduces the measured $Dl,CO$ by ~0.8–1% from both effects [13, 14]. Using this approach, the following equation empirically reduces predicted $Dl,CO$ by 1% for each per cent COHb ~2%:

$$Dl,CO,\text{predicted for COHb} = Dl,CO,\text{predicted} \times (102\% - \text{COHb}\%)$$ (18)

An adjustment for COHb is not required, but is recommended for interpretative purposes when COHb is elevated/suspected. No adjustment is required if COHb <2%, since reference equations already incorporate this.

Adjustment for lung volume

As noted previously, $Dl,CO$ decreases as the lung deflates as a function of both membrane and capillary configuration changes [17–24, 104–111]. The relationship is complex, however, and is probably nonlinear [108, 110]. In normal subjects with experimental reductions in $V_I$ (and, thus, $V_A$), adjustment equations for this effect have been derived [18, 19, 109, 111] and a recent representative example consists of the following:

$$Dl,CO (at V_{Am}) = Dl,CO (at V_{Ap}) \times (0.58 + 0.42(V_{Am}/V_{Ap}))$$ (19)

$$K_{CO (at V_{Am})} = K_{CO (at V_{Ap})} \times (0.42 + 0.58(V_{Am}/V_{Ap}))$$ (20)

where $V_{Am}$ represents measured $V_A$ and $V_{Ap}$ represents predicted $V_A$ at normal TLC.

It should be noted that this $Dl,CO$ adjustment for a reduced $V_I$ (and $V_A$) from a submaximal effort is substantially less than a 1:1 $Dl,CO/V_A$ adjustment (i.e. the fall in $Dl,CO$ as lung volumes are reduced is much less than the fall in $V_A$). As a consequence, the $Dl,CO/V_A$ ratio will rise with a reduced $V_I$ from a submaximal effort. Thus, if this ratio is used to adjust (“correct”) $Dl,CO$ for the effects of a reduced $V_A$ from a submaximal $V_I$, it will markedly “overcorrect”.

It is important to emphasise that the $V_A$ effects on $Dl,CO$ discussed above were derived from studies in normal subjects with submaximal $V_I$. These $V_A$ effects (and consequent $Dl,CO$ adjustments for $V_A$) have not been validated in lung diseases where lung pathology has reduced CO uptake properties, as well as $V_I$ and $V_A$. In some of these diseases (e.g. status post-pneumonecctomy), the reduction in $Dl,CO$ may be less than the reduction in $V_A$ (high $Dl,CO/V_A$); in others (e.g. pulmonary vascular disease), the reduction in $Dl,CO$ may be greater than the reduction in $V_A$ (low $Dl,CO/V_A$) [17]. In many disease states, however, the ratio of pathological reductions in $Dl,CO$ and $V_A$ may be quite variable and of unclear physiological or clinical significance. Thus, although the $Dl,CO/V_A$ relationship can be used to describe the relative reductions in CO uptake properties and alveolar gas volumes in lung disease [17, 19, 107, 112], drawing more specific clinical or pathological conclusions based upon $V_A$ (or any other volume) adjustments should be made with caution. This is especially true if the adjustment leads to the implication that CO uptake properties of the lung are normal. Further study is clearly needed on the interactions of CO uptake and alveolar gas volume in lung disease before more specific volume-adjustment recommendations can be made.

**Reporting values**

Several values are measured with the single-breath $Dl,CO$ and many factors affect $Dl,CO$. It is important that the report
includes the results needed for optimal interpretation. The average of at least two acceptable tests should be reported (i.e., outliers excluded).

The report should always include the unadjusted measured $D_{L,CO}$, the predicted and per cent predicted $D_{L,CO}$, and the predicted and per cent predicted $D_{L,CO}/VA$ (Kco). Any adjustments (e.g., for Hb, COHb, $P_{lO_2}$, or lung volume) should also be reported along with the data used to make the adjustment. The average $VA$ should be reported along with the predicted $VA$ (the predicted TLC minus predicted $VD$) and per cent predicted $VA$. The average $VI$ should also be noted. If a separately measured VC is available, it should be reported to serve as a reference for the adequacy of the $VI$. In addition, comments relevant to the quality of the measurements should be included.

### ABBREVIATIONS

Table 7 contains a list of abbreviations and their meanings, which will be used in this series of Task Force reports.

<table>
<thead>
<tr>
<th>Table 7</th>
<th>List of abbreviations and meanings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATPD</td>
<td>Ambient temperature, ambient pressure, and dry</td>
</tr>
<tr>
<td>ATPS</td>
<td>Ambient temperature and pressure saturated with water vapour</td>
</tr>
<tr>
<td>BTPS</td>
<td>Body temperature (i.e., 37°C), ambient pressure, saturated with water vapour</td>
</tr>
<tr>
<td>C</td>
<td>Centigrade</td>
</tr>
<tr>
<td>CFC</td>
<td>Chlorofluorocarbons</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetres</td>
</tr>
<tr>
<td>COHb</td>
<td>Carboxyhaemoglobin</td>
</tr>
<tr>
<td>$D_{L,CO}$</td>
<td>Diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor</td>
</tr>
<tr>
<td>$D_{L,CO}/VA$</td>
<td>Diffusing capacity for carbon monoxide per unit of alveolar volume, also known as Kco</td>
</tr>
<tr>
<td>$Dm$</td>
<td>Membrane-diffusing capacity</td>
</tr>
<tr>
<td>DT</td>
<td>Dwell time of flow &gt;90% of PEF</td>
</tr>
<tr>
<td>EFL</td>
<td>Expiratory flow limitation</td>
</tr>
<tr>
<td>ERV</td>
<td>Expiratory reserve volume</td>
</tr>
<tr>
<td>EV</td>
<td>Back extrapolated volume</td>
</tr>
<tr>
<td>EVC</td>
<td>Expiratory vital capacity</td>
</tr>
<tr>
<td>$F_{a,X}$</td>
<td>Fraction of gas X in the alveolar gas</td>
</tr>
<tr>
<td>$F_{a,1}$</td>
<td>Alveolar fraction of gas X at time t</td>
</tr>
<tr>
<td>FEF25–75%</td>
<td>Mean forced expiratory flow between 25% and 75% of FVC</td>
</tr>
<tr>
<td>FEFx%</td>
<td>Instantaneous forced expiratory flow when X% of the FVC has been expired</td>
</tr>
<tr>
<td>FEv1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FEv1</td>
<td>Forced expiratory volume in t seconds</td>
</tr>
<tr>
<td>$F_{1,X}$</td>
<td>Fraction of inspired gas X</td>
</tr>
<tr>
<td>FIFx%</td>
<td>Instantaneous forced inspiratory flow at the point where X% of the FVC has been inspired</td>
</tr>
<tr>
<td>$F_{1,L}$</td>
<td>Fraction of inspired gas X</td>
</tr>
<tr>
<td>FIVC</td>
<td>Forced inspiratory vital capacity</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>Water</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Hg</td>
<td>Mercury</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz; cycles per second</td>
</tr>
<tr>
<td>IC</td>
<td>Inspiratory capacity</td>
</tr>
<tr>
<td>IRV</td>
<td>Inspiratory reserve volume</td>
</tr>
</tbody>
</table>

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