The single-breath carbon monoxide diffusing capacity (DL\textsubscript{CO}) is the product of two measurements during breath holding at full inflation: (1) the rate constant for carbon monoxide uptake from alveolar gas (k\textsubscript{CO} [minute\textsuperscript{-1}]) and (2) the "accessible" alveolar volume (VA). k\textsubscript{CO} expressed per mm Hg alveolar dry gas pressure (P\textsubscript{b}*), and then multiplied by VA, equals DL\textsubscript{CO}, thus, DL\textsubscript{CO} divided by VA (DL\textsubscript{CO}/VA, also called KCO) is only k\textsubscript{CO}/P\textsubscript{b}* in different units, remaining, essentially, a rate constant. The notion that DL\textsubscript{CO}/VA "corrects" DL\textsubscript{CO} for reduced VA is physiologically incorrect, because DL\textsubscript{CO}/VA is not constant as VA changes; thus, the term KCO reflects the physiology more appropriately. Crucially, the same DL\textsubscript{CO} may occur with various combinations of KCO and VA, each suggesting different pathologies. Decreased KCO occurs in alveolar–capillary damage, microvascular pathology, or anemia. Increased KCO occurs with (1) failure to expand normal lungs to predicted full inflation (extrapulmonary restriction); or (2) decreased capillary volume and flow, either globally (left-to-right intracardiac shunting) or from flow and volume diversion from lost or damaged units to surviving normal units (e.g., pneumonectomy). Decreased VA occurs in (1) reduced alveolar expansion, (2) alveolar damage or loss, or (3) maldistribution of inspired gases with airflow obstruction. KCO will be greater than 120% predicted in case 1, 100–120% in case 2, and 40–120% in case 3, depending on pathology. KCO and VA values should be available to clinicians, as fundamental to understanding the clinical implications of DL\textsubscript{CO}. The diffusing capacity for nitric oxide (DL\textsubscript{NO}), and the DL\textsubscript{NO}/DL\textsubscript{CO} ratio, provide additional insights.

Keywords: diffusing capacity for carbon monoxide (DL\textsubscript{CO}); diffusing capacity for nitric oxide (DL\textsubscript{NO}); DL\textsubscript{CO}/VA (KCO); pulmonary function tests; alveolar gas exchange

The single-breath diffusing capacity for carbon monoxide (DL\textsubscript{CO}) (known in Europe as the transfer factor, T\textsubscript{LCO}) is, after spirometry and lung volumes, the most clinically useful pulmonary function test. The DL\textsubscript{CO}, as pointed out by its originator, Marie Krogh (1), is the product of two separate but simultaneous measurements (Figure 1): the rate constant k\textsubscript{CO} (the rate of uptake of CO from alveolar gas), and the alveolar volume (VA). The important point is that KCO (k\textsubscript{CO} reexpressed per mm Hg alveolar PCO) is linearly related to the alveolar uptake efficiency for carbon monoxide (2, 3). Because of the special properties of carbon monoxide, KCO directly reflects the quality of alveolar-capillary gas uptake. Many articles and pulmonary function testing (PFT) laboratories do not quote VA and KCO from which the DL\textsubscript{CO} is derived; this may result in significant loss of clinical information.

**MEASUREMENT OF KCO AND VA**

**Rate of Uptake of Alveolar Carbon Monoxide (k\textsubscript{CO})**

During breath holding in the single-breath DL\textsubscript{CO}, CO is removed from alveolar gas at an exponential rate [log\textsubscript{e}(CO\textsubscript{0}/CO\textsubscript{t})/BHT], where CO\textsubscript{0} and CO\textsubscript{t} are the alveolar concentrations at the start and finish of the breath-holding time (BHT). This expression is a rate constant with units of minute\textsuperscript{-1} or second\textsuperscript{-1}; in Figure 1 it is represented by the slope, kCO.

**Alveolar Volume (VA)**

The DL\textsubscript{CO} is measured during breath holding at full inflation; in absolute terms, this represents total lung capacity (TLC). The lung volume during breath holding is measured simultaneously by dilution of any nonabsorbable gas, most commonly helium (He) (Figure 1), at the same time as the k\textsubscript{CO} is measured (4). The alveolar volume (VA) is an "accessible" volume, that is, that seen by the gas-exchanging surface, derived from the single-breath helium dilution volume after subtracting an "estimated" anatomic dead space (V\textsubscript{d\textsubscript{anat}}) from the inspired volume (V\textsubscript{i}) (Figure 1). The V\textsubscript{i} starts from residual volume and finishes at maximal inflation (~TLC); the inspiration should be made as rapidly as possible. In normal subjects, VA is within 10% of TLC, with a mean VA/TLC ratio (combining men and women) of 93.5% ± 6.6 (1 SD) (5); the VA/TLC ratio has no significant dependence on age, sex, height, or weight (5), but decreases substantially when there is intrapulmonary airflow obstruction and maldistribution of ventilation. V\textsubscript{d\textsubscript{anat}} represents 2-3% of the TLC in normal subjects, the remaining 4% of the VA/TLC difference occurring because gas mixing in the 10-second breath hold is incomplete. In disease, the difference between the single-breath VA and the multibreath or plethysmographic TLC, and the VA/TLC ratio, deserves more study (5) as an index of gas mixing efficiency.

**Combining VA and kCO**

Equation 1 is the first step in the calculation of the DL\textsubscript{CO}:

\[
\text{VA} \times k\text{CO} = V\text{CO}
\]

\[
\text{ml (STPD)} \times \text{min}^{-1} = \text{ml min}^{-1},
\]

where k\textsubscript{CO} is the fractional change in CO concentration, expressed in minute\textsuperscript{-1} and V\textsubscript{CO} is the uptake of CO from alveolar gas during breath holding at TLC. Equation 1 gives a large value for V\textsubscript{CO} because, as pointed out by Marie Krogh (1), the calculation implies that all alveolar gas is pure CO. For the second step, to obtain DL\textsubscript{CO}, both sides of the equation are divided by P\textsubscript{b*}, where P\textsubscript{b*} is

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**Author Contributions**

This review was conceived by J.M.B.H., who drafted the text, illustrations, and tables. N.B.P. contributed to discussion and modification of the concept, design, and interpretation; both authors have approved the final version.

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Figure 1. Carbon monoxide (CO) and helium (He) kinetics in the single-breath DLCO. Concentrations of the marker gases CO and He after rapid inspiration from residual volume to TLC, plotted against breath hold time, showing the origin and calculation of the components (kco and Vco) from which DLco is derived. Definitions of abbreviations: BHT = breath-holding time; COo, COa = alveolar concentration of CO at the start and finish of the breath-holding time, respectively; COi = inspired concentration of carbon monoxide; DLco = carbon monoxide diffusing capacity; He, HET = inspired and expired concentrations of inert marker gas helium, respectively; kco = rate constant for carbon monoxide uptake; Kco = rate constant for carbon monoxide uptake per unit barometric pressure (kco/Pbo ~ DLco/Vco); Vco = alveolar volume; Vbi = inspired volume; Vbainat = anatomical dead space. Calculations: The rate constant kco equals log2((COo/COa)/BHT); for points t = 0 and t = 10 seconds and gas concentrations as fractions (not %), kco = log2(0.35/0.16)/10 = 0.08 second1 or (x 100) 8% per second or (x 60) 4.8 minute1; kco/Pbo = 4.8/713 = 0.0067 minute1 mm Hg1. For Vco 5,000 (ml STPD), DLco = kco/Pbo × Vco = 5,000 × 0.0067 = 33.5 ml minute1 mm Hg1; Kco = DLco/Vco BTPS = 33.5/(5,000 × 1.2/1,000) = 5.58 ml minute1 mm Hg1 L1. The ratio Kco/kco = 1.16, and Kco/kcoPbo = 883.

barometric pressure, usually approximately 760 mm Hg, minus water vapor pressure at 37 C in alveolar gas (Pb – PH2O), Thus:

\[ \frac{Vco}{kco} \times \frac{Pb}{Vbi} = DLco \]  

(2)

where Vco/Pbo is the alveolar CO uptake per minute per ml Hg Pco, which, as a conductance, defines the DLco. In pulmonary function reports DLco is divided by Vco with ml STPD exchanged for L BTPS:

\[ DLco/Vco BTPS = [kco/Pbo] \times 1000/1.2 = Kco, \]  

(3)

where DLco/Vco and Kco have units of minute1 mm Hg1 L1, 1,000 converts milliliters to liters, and 1.2 is the STPD-to-BTPS factor. These units, as reported in pulmonary function laboratories, give the impression of a volume “adjustment,” leading to much confusion, whereas it is obvious from equation 3 that kco (the rate constant) only differs from DLco/Vco (= Kco) by three constant factors (Pbo, 1,000, and 1.2) and in its units. The ratios DLco/Vco (= Kco) to kco and to kco/Pbo (both constant except for minor variations in Pbo) are given in the legend to Figure 1. Therefore, DLco/Vco (= Kco) is effectively the rate constant, representing alveolar carbon monoxide uptake efficiency. Unless required by the context, this review uses the term Kco in preference to DLco/Vco.

WHAT DOES THE KCO SIGNIFY?

The previous section has shown that kco (second1 or minute1), kco/Pbo (minute1 mm Hg1), and DLco/Vco (= Kco) (ml minute1 mm Hg1 L1 BTPS) are physiologically equivalent, except in their units, to the rate of removal of CO from alveolar gas, that is, the slope (on a semilogarithmic plot) of carbon monoxide uptake in Figure 1, labeled kco. Kco, expressed as kco, is the rate constant for alveolar CO uptake; Kco, expressed as DLco/Vco, is the carbon monoxide diffusing capacity per unit alveolar volume, at the alveolar volume (Vco) at which the measurement is made; it remains, in essence, a pressure-adjusted rate constant for alveolar carbon monoxide uptake. The difficulty, or confusion, stems from the notion that “per unit volume” implies DLco corrected for lung volume, a concept that is wrong because DLco measured at a different volume, at a different level of Vco/VA, would yield a different value for DLco/Vco (= Kco) (see Figures 2 and 3). Paradoxically, DLco/Vco contains no information about the value of Vco, being a weighted mean value of the rate of CO uptake in the “accessible” Vco. Therefore, it would be prudent to replace the misleading (although physiologically correct) “diffusing capacity per unit alveolar volume” by Kco, which, unlike the earlier term kco, is numerically the same as DLco/Vco.

How should the Kco be defined? Krogh (1) called k (= kco) “permeability,” and Kco has been referred to as the Krogh factor (6). Cotes (7) and others (8) refer to Tlco/Vco (= DLco/Vco) as the “transfer coefficient.” Hughes and Pride (2) referred to Kco as “essentially the rate constant for alveolar CO uptake.” No clarifying definition has emerged from the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on Standardization of Lung Function Testing (9, 10), who still refer to Kco or DLco/Vco, like most authors, as “diffusing capacity per unit alveolar volume.” We regard the Kco as an index of the efficiency of alveolar transfer of carbon monoxide (approximately the rate of CO uptake); “transfer” is a better term than “diffusion” because of the importance of the reaction rate of carbon monoxide with pulmonary capillary blood (see Equation 4). Nevertheless, “rate constant for carbon monoxide uptake” is probably the best operational definition for the Kco.

DETERMINANTS OF KCO IN NORMAL SUBJECTS

Effect of Lung Volume

As the lung volume decreases from TLC to FRC, the DLco falls and Kco rises (8, 11) (Figure 2). Expressed as a percentage of the value at predicted TLC (~Vmax), DLco at 50% Vmax is 79%, and Kco is 158% (8). This increased efficiency of alveolar uptake of carbon monoxide (Kco) at resting breathing volumes protects the DLco against undue volume dependence, that is, DLco is 80% of its TLC value at 50% Vmax rather than the expected 50%. The physiological reason for the increase in Kco with decreasing alveolar expansion is given in the Roughton–Forster (12) equation (1/DLco = 1/DMco + 1/0-Vc), normalized to VA:

\[ VA/DLco = 1/Kco = VA/DMco + VA/θhuco · Vc, \]  

(4)

where Dv is the membrane diffusing capacity; θhuco is the reaction rate of carbon monoxide with blood (minute1 mm Hg1); adjusted to a standard hemoglobin (Hb) concentration; and Vc is the pulmonary capillary volume. With a decrease in alveolar expansion, the ratio VA/Dm remains almost constant (13), so the fall in VA/DLco (= rise in Kco) is caused by the decrease in VA/Vc (= rise in Vc/Va), with Vc remaining constant as VA decreases (13). The change in Vc/Va is consistent with the stability of pulmonary blood flow (approximately the cardiac output) during lung volume changes.

Changes on Exercise

During exercise, DLco (and Kco) rises at constant VA (14). This was first shown by M. Krogh in 1915 (1). The reason is that the rise of pulmonary artery (and, to a lesser extent, pulmonary
venous) pressure, which accompanies the increase in pulmonary blood flow, distends the pulmonary capillary bed and recruits additional alveolar septal vessels (15). This increases capillary volume (Vc) and the membrane diffusing capacity (Dm) (14).

On exercise at constant VA, Vc/VA increases; Dm/VA also increases because vascular distension expands the alveolar surface available for gas exchange. Thus, DLCO/VA (Kco) increases. With the rebreathing technique, usually used in exercise studies for measuring DLCO (14), mean VA does not change from rest to exercise (14, 16), being mostly constrained by the volume of the rebreathing bag, but VA did increase on exercise according to the open-circuit DLCO method (16); in this case, the increase in VA would itself contribute to the increase in DLCO, although its effect would be reduced by a fall in Kco accompanying the rise in VA.

Variables That Can Be Controlled

Other factors that influence Kco (but not VA) are anemia and alveolar PO2 because the partitioning of flow between the two lungs, and assuming total pulmonary blood flow (cardiac output) remains the same at rest to 10 L (minute); that is, in an average case to 120% predicted (98 + 22%).

The highest values for Kco have been found in boys and girls (6), suggesting that the pulmonary capillary bed has developed earlier than alveolar volume. The decline in Kco in adults with age may be related to changes in the microvasculature, secondary to the loss of lung elasticity with aging. The inverse relationship with height for Kco may be because the apices of the lungs are less well perfused in the upright position in taller people for gravitational reasons. There is considerable scatter in the predicted values for different reference equations for DLCO and Kco, and there is no consensus on the “best choice” (10). Thus, there is a need to acquire new reference values for DLCO and for its components. The European Standardization Working Party (17) recommends that Kco (predicted) be calculated as DLCO (predicted)/TLC (predicted), from measurements made at different times and often in different places. Predicted values for Kco would be better based on the two simultaneous measurements, that is, from DLCO divided by single-breath “accessible” VA rather than from two separate procedures (DLCO and TLC).

Nomenclature and Units

This review refers to the DLCO as the carbon monoxide diffusing capacity, and uses traditional units (ml and mm Hg). In Europe, the DLCO is termed the “carbon monoxide transfer factor” (TLCO) and SI units are used for gas uptake (mmol) and pressure (kPa). Divide by 3.0 to convert traditional to SI units.

Changes in Kco and “Accessible” Va in Disease

Clinical Causes of Decreases or Increases in Kco

Alveolar and/or microvascular damage and destruction, leading to loss of alveolar or capillary surface area, affecting both Dm and Vc, reduce the rate of carbon monoxide uptake per unit volume, leading to a low Kco as a percentage of the predicted value; in some circumstances, Kco may exceed the upper limit of normal at predicted TLC, and this has clinical significance (Table 1) (19–32).

In relation to increases in Kco, incomplete alveolar expansion, without compromise of alveolar structure, elevates Kco by increasing Vc/VA; a lesser increase in Vc/VA is also largely responsible for the increase in Kco with increases in pulmonary blood flow, either through the whole lung, as in a left-to-right shunt, or through part of the lung, as after a pneumonectomy. The increase in Kco (and also DLCO) in asthma is probably linked to better perfusion of the apices of the lungs (27), and this may explain, in part, the increase in Kco in some obese patients, although a raised capillary volume and low Dm have been found (33), suggesting an element of pulmonary venous congestion as in chronic heart failure (34, 35).

Diversion of blood flow from a resected lung, for example, pneumonectomy, increases perfusion per unit volume in the remaining lung by 80–100%, depending on the preoperative partitioning of flow between the two lungs, and assuming total pulmonary blood flow (~cardiac output) remains the same posts pneumonectomy. This will increase the Kco in the lung that remains. Corris and colleagues (30) established an empirical relationship in 28 patients for the increase in Kco that occurred posts pneumonectomy:

\[ \Delta \text{Kco} \text{% predicted} = 0.4x + 2.1, \]

where x was the percentage flow (%) to the resected lung, based on a preoperative radioisotope lung perfusion scan. Kco post-pneumonectomy was 110–131% predicted (mean Kco preoperatively for both lungs averaged 98%); in the case in which flow to both lungs was equal preoperatively (x = 50%), Equation 5 predicts the Kco in the remaining nonresected lung to increase by +22%, that is, in an average case to 120% predicted (98 + 22%). The reason for this increase in Kco is the expected doubling of blood flow per unit volume in the remaining lung. This \( \Delta \text{Kco} \) is consistent with the 20% increase in Kco when pulmonary blood flow in normal lungs increases from 5 L minute \(^{-1}\) at rest to 10 L minute \(^{-1}\) on moderate exercise (14). Va after pneumonectomy averaged 50% of the preoperative value; thus, the remaining lung was expanded to its predicted TLC when the Kco was measured.
postoperatively. Note that for a similar reduction of overall VA to 50% predicted, but applied to both lungs by underexpansion (e.g., neuromuscular disease), the increase in KCO at 50% VA/VATLC is considerably greater (158%: see Figure 2) than the 122% occurring postpneumonectomy.

The effect of 50% volume loss from two different causes, (1) reduced alveolar expansion and (2) “loss of units” (pneumonectomy), is illustrated for DLCO in Figure 3A and for KCO in Figure 3B. The difference for KCO in Figure 3B arises from different changes in the two components of the KCO from the Roughton–Forster formula (Equation 4), VA/DM and VA/Vc. With restricted alveolar expansion, DM/VA (inverse of VA/DM) and Vc (13) remain relatively constant; hence halving lung volume (to 50% VA/VATLC) will increase Vc/VA to 200% and increase KCO to 158% (Figure 3B). After pneumonectomy, the whole cardiac output must be distributed to the remaining lung whose blood flow, per unit volume, probably doubles. A doubling of pulmonary blood flow during moderate exercise in normal subjects increases the KCO to 120%; this arises from changes in both the DM and Vc components of the Roughton–Forster equation: DM/VA increases to 133% and Vc/VA to 141% of their resting values (14). The larger increase in Vc/VA at 50% VA/VATLC with underexpansion (200%) compared with exercise (141%), and, by implication, postpneumonectomy may arise because the number of alveoli and alveolar capillaries in two lungs is twice the number postpneumonectomy.

Clinical causes of a low “accessible” alveolar volume (VA)

In the single-breath DLCO, there are three distinct causes of a low VA (as a percentage of VAm peak predicted, ~93.5% ± 6.6

| TABLE 1. PATHOPHYSIOLOGY AND CLINICAL EXAMPLES OF AN ABNORMAL KCO |
|--------------------|------------------|
| **Mechanism**       | **Clinical Examples** |
| Microvascular destruction | Idiopathic pulmonary hypertension (19) |
| Microvascular remodeling and dilation | Pulmonary vasculitis (20) |
| Microvascular remodeling and dilation | Hepatopulmonary syndrome (21, 22) |
| Alveolar destruction | Pulmonary arteriovenous malformations (23) |
| Alveolar destruction | Emphysema (low “accessible” VA) |
| Alveolar destruction | Diffuse interstitial lung disease with fibrosis |
| Alveolar destruction | Bronchiolitis obliterans (24) |
| Alveolar destruction | Chronic heart failure (severe) (25) |
| Alveolar destruction | Incomplete alveolar expansion to TLC |
| Alveolar destruction | Increased pulmonary blood flow |
| Alveolar destruction | Microvascular destruction |
| Alveolar destruction | Microvascular destruction |
| Alveolar destruction | Microvascular destruction |
| Alveolar destruction | Inspiratory muscle weakness (28) |
| Alveolar destruction | Chest wall restriction (29) |
| Alveolar destruction | Poor cooperation or comprehension |
| Alveolar destruction | Pneumonectomy (30) |
| Alveolar destruction | Obesity (31) |
| Alveolar destruction | Anti-GBM disease (32), SLE |

**Definition of abbreviations:** GBM = glomerular basement membrane; SLE = systemic lupus erythematosus.

Clinical examples are not an exhaustive list.
1. Incomplete alveolar expansion (Kco > 120% predicted).
2. Loss of lung units (Kco 100–120% predicted). Besides pneumonectomy, localized destruction of lung units fibrosis, infiltration with granulomas or inflammatory exudates, atelectasis, alveolar edema, and pneumonic consolidation are other causes.
3. Poor mixing with maldistribution of inspired gas. This is most obvious in the case of a bulla. But, intrapulmonary airflow obstruction from any of the major causes (emphysema, bronchitis, bronchiolitis, bronchiectasis, asthma) generally lowers the VA/TLC ratio, when VA is measured with 10-second helium dilution and TLC with body plethysmography or multibreath inert gas wash-in or washout (4). VA, even in normal subjects, is an “accessible” rather than an absolute volume. The Kco is variable and depends on the pathology (Table 2). But, clearly there is a continuum in the sense of different values of VA and Kco within a single diagnostic category.

These three causes may coexist: causes 1 and 2 in interstitial lung disease, and causes 2 and 3 in COPD or bronchiectasis.

Kco ENHANCES UNDERSTANDING OF DLco

The DLco is the product of its two components, Kco and VA (Equation 1). The most compelling argument in favor of the Kco (unadjusted) is set out in Table 3, where the same value of DLco (as a percentage of the predicted value) may occur from different combinations of its components (Kco and VA). The combination of low VA and high Kco has a different clinical significance (extrapulmonary restriction) compared with the combination of low Kco and normal VA (microvascular injury), although the DLco is practically the same.

In chronic inspiratory muscle weakness (28, 39), the Kco is usually less (120–130%) (Table 3, diagnosis A) than that predicted from the decrease of VA (Kco predicted would be 150%; Figure 3B), presumably due to secondary changes stemming from microatelectasis, retention of secretions, and infection. In interstitial lung disease (Table 3, diagnosis C), especially preceding the overt fibrotic phase, the Kco may be within the “normal” range (say 80–100%), but in the presence of a low VA, this could be interpreted as “abnormal” because the expected compensation via the “loss of units” model is lacking. In emphysema (in this example) (Table 3, diagnosis D) there is relatively little gas mixing deficit after inspiration to TLC, and Kco predicted is less than VA predicted, suggesting disorganization of peripheral airspace, which remain (mostly) ventilated. This contrasts with Table 3, diagnosis C, in which the DLco is similar, but Kco is higher than the VA. This suggests that the disease is more localized with up to 30% of alveolar units destroyed or infiltrated with inflammatory exudate (gas mixing from the VA/TLC ratio [data not shown] is normal), and that the remaining alveolar units are functioning well, even if not entirely normally, as gas exchange units. The analysis adds less in Table 3, diagnosis E, in which a low DLco in the presence of normal lung volumes without airflow obstruction suggests a different pulmonary vascular pathology.

CURRENT VIEWS ON DLco/VA (= Kco)

In an earlier section (MEASUREMENT OF Kco AND VA: COMBINING VA AND KCO) we pointed out that current practice reports DLco/VA (= Kco) literally as DLco divided by VA with units ml minute⁻¹ mm Hg⁻¹ L⁻¹; this redundancy of units (the units of DLco/VA and Kco are essentially minute⁻¹ mm Hg⁻¹, that is, kco/Pb *; see Equation 2) has led to the idea that DLco/VA “adjusts” or “corrects” the DLco when the VA is lower than predicted. Because DLco/VA (= Kco) is not a constant function versus VA (Figures 2 and 3), several authors (40–42) have claimed that DLco/VA has no clinical value, and even that the Kco is an “arithmetically flawed” index (7) (if this were the case, we would expect Kco × VA = DLco/VA to share this flaw). The confusion arises from the substitution for Kco of its equivalent (DLco/VA), which gives the impression of a “volume correction.” The ATS/ERS Task Force (9, 10) counsels caution in the use of the DLco/VA ratio, but nowhere is the connection made that the DLco/VA is essentially a rate constant, similar to kco and kco/Pb * except in its units. It is clear that the nonlinear relationship between Kco and lung volume (Figure 2) precludes DLco/VA from being a “volume correction” for the DLco when VA is reduced, but Kco remains a true reflection of alveolar CO uptake efficiency at a given volume. In our opinion, the emphasis on DLco/VA as a correction factor for lung volume is misconceived, and reflects a misapprehension of the physiology. Hence, we believe the term DLco/VA should be replaced by the more informative term, Kco.

SHOULD THE Kco BE CORRECTED FOR A LOW VA?

Corrections have been proposed on the basis of the relationship in normal subjects between change of lung volume and the change in DLco/VA (Kco). A typical relationship (data from 24 subjects) is as follows (8):

$$\frac{DLco}{DLco_{TLC}} = 0.58 + 0.42 \times \frac{VA}{V_{ATLC}}.$$  \(6\)

where DLco_{TLC} and V_{ATLC} are expected values for DLco and VA at a normal predicted TLC. For a VA/V_{ATLC} ratio of 0.5,
DLCO would be multiplied by 1.26 to adjust for the volume reduction. The relationship for KCO was

$$\text{KCO}/\text{KCO}_{\text{TLC}} = 0.43 + 0.57(\text{VA}/\text{VA}_{\text{TLC}})$$  \(7\)

Thus, KCO would be adjusted down at 0.5 VA/VA_{TLC} by multiplying by 0.64 (1/1.57). Johnson (8) studied retrospectively the pulmonary function records of 2,313 patients, and analyzed subgroups of patients with asthma, emphysema, extrapulmonary restriction, interstitial lung disease, and lung resection. Before adjustment, there was wide dispersion between DLCO and KCO in extrapulmonary restriction than after a pneumonectomy (48). Unlike DLCO, DLNO is PO2 independent (48). The low red cell resistance suggests that DLNO is measuring mostly the diffusive component of the alveolar to red cell transfer pathway, related to the surface area/thickness ratio of the blood gas barrier. Since the work of Roughton and Forster (12) this has been referred to as the membrane diffusing capacity (DM). DMNO is related to the better known DMCO by \(\alpha = 1.97\), the ratio of the physical diffusivities of nitric oxide and carbon monoxide in plasma, that is, DMNO/\(\alpha = \text{DMCO}\). Guenard and colleagues (45) measured DLNO and DLCO simultaneously by the classical single-breath technique. Assuming DMNO/\(\alpha = \text{DMCO}\), they showed that the Roughton–Forster formula (1/DLNO = 1/DMCO + 1/\(\theta_{\text{blCO}}\)) could be rearranged:

$$1/\text{Vc} = \theta_{\text{blNO}}/(1/\text{DLNO} - \alpha/\text{DLNO})$$  \(8\)

Reasonable values of DMCO and Vc were obtained in normal subjects (45).

Although, for clinical interpretation, DLNO may be regarded as a surrogate for the membrane diffusing capacity (DM), the notion that \(\theta_{\text{blCO}}\) is infinite has been called into question. Measurements of DLNO before and after experimentally induced hemolysis (49) and after blood substitution, in anesthetized dogs, with cell-free heme-based oxyglobin (50), suggest that DLNO is not entirely “red cell independent.” After oxyglobin exchange transfusion, in the red cell–free state, DLNO increased 1.5 times (DLCO did not change), which suggests that DMNO is 1.5 times DLNO rather than its equivalent. It was suggested previously that DLNO might be a surrogate for DLNO (51).

### THE DLNO/DLCO RATIO

Because of reservations about the relevance of in vitro measurements of \(\theta_{\text{blCO}}\) and \(\theta_{\text{blNO}}\) to the in vivo situation (49, 50), interest is shifting from estimates of DM and Vc toward the DLNO/DLCO ratio. Assuming, for clinical purposes, that \(\theta_{\text{blCO}}\) is infinite so that DLNO = DMNO = DMCO/\(\alpha\), and from the Roughton–Forster equation for carbon monoxide (12):

$$\text{DLNO}/\text{DLCO} = \alpha (1 + \text{DMCO}/\theta_{\text{blCO}} - \text{Vc})$$  \(9\)

Thus, the DLNO/DLCO ratio is weighted toward the DM/Vc ratio and \(\alpha\) (the NO/CO physical solubility ratio). It is also equivalent
to the KNO/KCO ratio because DL = K × VA, and VA is common to DlNO and DlCO when measured simultaneously by the standard single-breath technique with inhalation of nitric oxide and carbon monoxide. Measurements of the DlNO/DlCO ratio have been performed in normal subjects, at rest and during exercise (53–55), and over a range of lung volumes (56, 57). The DlNO/DlCO ratio has been studied in several clinical situations. For example, the DlNO/DlCO ratio is increased in heavy smokers (58), otherwise healthy, and in diffuse parenchymal disease (59) and in chronic thromboembolic pulmonary hypertension (59), possibly because Vc/VA is reduced more than Dm/VA. In contrast, the DlNO/DlCO ratio is decreased at FRC versus TLC (56), the explanation being that DlNO is more sensitive to alveolar under-expansion than DlCO. For example, from Vatlc to Vas0% TLC the DlNO declines by 43% versus 29% for DlCO (56). The reason is that the fall in DlCO is buffered by an increase in KCO (+35%) whereas KNO (being less influenced by the rise in Vc/VA) increases by only 10% (56). Thus, the DlNO/DlCO ratio could become a marker for extrapulmonary restriction.

The DlNO/DlCO ratio gives some insights into the components (Dm and Vc) of the Roughton–Forster equation in a single maneuver without the two-step approach with carbon monoxide at different alveolar Po2 as well as by-passing Dblood, the value of which is somewhat controversial (51, 52). Experience to date with Dm and Vc partitioning has been disappointing because commonly both change equally (the only notable example of discordance [Dm↑, Vc↑] being chronic heart failure [34, 35]); thus, we would expect a low DlNO/DlCO ratio in chronic heart failure, at least in the early stages. It is also possible that by factoring out VA, the DlNO/DlCO ratio (= KNO/KCO) may provide additional insight into other respiratory diseases.

CONCLUSIONS

The single-breath DlCO is, physiologically, the product of two simultaneous measurements: the rate of carbon monoxide uptake from alveolar gas to pulmonary capillary blood (kco), reexpressed per mm Hg alveolar dry gas pressure (Pb*) as kco/Pb*, and the “accessible” alveolar volume (VA), which approaches, in normal subjects, TLC. kco/Pb* is linked mathematically to DlCO/VA (= KCO). The term DlCO/VA is misleading because, as kco/Pb*, it reflects the rate of alveolar uptake of CO.

The common causes of a low VA are (1) underexpansion of alveoli in relation to their predicted TLC, (2) loss of alveolar units by destruction or infiltration with exudates or transudates, (3) poor gas mixing and penetration during the 10-second single-breath maneuver, and (4) some combination of cases 1, 2, and 3. Thus, there is no single factor or equation with which the pulmonary function laboratory can “correct” or “adjust” DlCO for all the causes of a low VA, and the use of the term DlCO/VA should be replaced by its alternative, KCO.

Clinical interpretation of a low DlCO (as a percentage of the predicted value) stems from inspection of the components of the DlCO (KCO and VA) and knowledge of physiological principles. From a consideration of the KCO and VA (as a percentage of the predicted value), together with spirometry and lung volume measurements, it should be possible to distinguish emphysema from bronchiectasis, bronchiectasis from asthma, diffuse interstitial lung disease from extrapulmonary restriction, and both from pulmonary microvascular disease.

In the future, the diffusing capacity for nitric oxide (DlNO) may enable us to focus on alveolar structure differently from the DlCO. The DlNO/DlCO ratio may be a surrogate for the Dm/Vc ratio and DlNO may provide information on total barrier (tissue and blood) thickness, largely independent of any chemical resistance introduced by the presence of hemoglobin.

References


51. Hughes JMB, Bates DV. Historical review: the carbon monoxide diffusing capacity ($D_{LCO}$) and its membrane ($D_{M}$) and red cell ($V_{C}$) components. Respir Physiol Neurobiol 2003;138:115–142.


