Concise Clinical Review

Examination of the Carbon Monoxide Diffusing Capacity (D_{LCO}) in Relation to Its K_{CO} and V_A Components

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The single-breath carbon monoxide diffusing capacity (D_{LCO}) is the product of two measurements during breath holding at full inflation: (*1*) the rate constant for carbon monoxide uptake from alveolar gas (k_{CO} [minute^{-1}]) and (*2*) the "accessible" alveolar volume (V_A). k_{CO} expressed per mm Hg alveolar dry gas pressure (Pb*) as k_{CO}/Pb*, and then multiplied by V_A, equals D_{LCO}; thus, D_{LCO} divided by V_A (D_{LCO}/V_A, also called K_{CO}) is only k_{CO}/Pb* in different units, remaining, essentially, a rate constant. The notion that D_{LCO}/V_A "corrects" D_{LCO} for reduced V_A is physiologically incorrect, because D_{LCO}/V_A is not constant as V_A changes; thus, the term K_{CO} reflects the physiology more appropriately. Crucially, the same D_{LCO} may occur with various combinations of K_{CO} and V_A, each suggesting different pathologies. Decreased K_{CO} occurs in alveolar–capillary damage, microvascular pathology, or anemia. Increased K_{CO} occurs with (*1*) failure to expand normal lungs to predicted full inflation (extrapulmonary restriction); or (*2*) increased 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 V_A occurs in (*1*) reduced alveolar expansion, (*2*) alveolar damage or loss, or (*3*) maldistribution of inspired gases with airflow obstruction. K_{CO} will be greater than 120% predicted in case 1, 100–120% in case 2, and 40–120% in case 3, depending on pathology. K_{CO} and V_A values should be available to clinicians, as fundamental to understanding the clinical implications of D_{LCO}. The diffusing capacity for nitric oxide (D_{LNO}), and the D_{LNO}/D_{LCO} ratio, provide additional insights.

Keywords: diffusing capacity for carbon monoxide (D_{LCO}); diffusing capacity for nitric oxide (D_{LNO}); D_{LCO}/V_A (K_{CO}); pulmonary function tests; alveolar gas exchange

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

MEASUREMENT OF K_{CO} AND V_A

Rate of Uptake of Alveolar Carbon Monoxide (k_{CO})

During breath holding in the single-breath D_{LCO}, CO is removed from alveolar gas at an exponential rate $[\log_e(CO_0/CO_t)/BHT]$, where CO_0 and CO_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^{-1} or second^{-1}; in Figure 1 it is represented by the slope, k_{CO}.

Alveolar Volume (V_A)

The D_{LCO} 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_{CO} is measured (4). The alveolar volume (V_A) 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_{Danat}) from the inspired volume (V_I) (Figure 1). The V_I starts from residual volume and finishes at maximal inflation (~TLC); the inspiration should be made as rapidly as possible. In normal subjects, V_A is within 10% of TLC, with a mean V_A/TLC ratio (combining men and women) of 93.5% ± 6.6 (1 SD) (5); the V_A/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_{Danat} represents 2–3% of the TLC in normal subjects, the remaining 4% of the V_A/TLC difference occurring because gas mixing in the 10-second breath hold is incomplete. In disease, the difference between the single-breath V_A and the multibreath or plethysmographic TLC, and the V_A/TLC ratio, deserves more study (5) as an index of gas mixing efficiency.

Combining V_A and k_{CO}

Equation 1 is the first step in the calculation of the D_{LCO}:

$$V_A \times k_{CO} = \dot{V}_{CO} \qquad (1)$$

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

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

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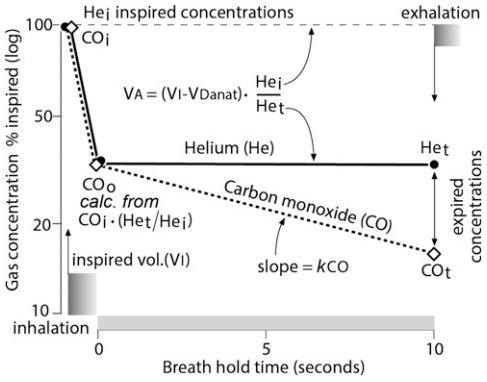

Figure 1. Carbon monoxide (CO) and helium (He) kinetics in the single-breath D_{LCO}: concentrations of the marker gases CO and He after rapid inspiration from residual volume to TLC, plotted against breath hold time, showing the origin and calculation of the components (kCO and V_A) from which D_{LCO} is derived. *Definitions of abbreviations*: BHT = breath-holding time; CO_0, CO_t = alveolar concentration of CO at the start and finish of the breath-holding time, respectively; CO_i = inspired concentration of carbon monoxide; D_{LCO} = carbon monoxide diffusing capacity; He_i, He_t = 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/Pb* ~ D_{LCO}/V_A); V_A = alveolar volume; V_I = inspired volume; V_{Danat} = anatomical dead space. *Calculations*: The rate constant kCO equals $\log_e(CO_0/CO_t)$/BHT; for points t = 0 and t = 10 seconds and gas concentrations as fractions (not %), kCO = $\log_e(0.35/0.16)/10$ = 0.08 second^{-1} or (× 100) 8% per second or (× 60) 4.8 minute^{-1}. kCO/Pb* = 4.8/713 = 0.0067 minute^{-1} mm Hg^{-1}. For V_A 5,000 (ml STPD), D_{LCO} = kCO/Pb* × V_A = 5,000 × 0.0067 = 33.5 ml minute^{-1} mm Hg^{-1}. KCO = $D_{LCO}/V_{A\,BTPS}$ = 33.5/(5,000 × 1.2/1,000) = 5.58 ml minute^{-1} mm Hg^{-1} L^{-1}. The ratio KCO/kCO = 1.16, and KCO/(kCO/Pb*) = 883.

barometric pressure, usually approximately 760 mm Hg, minus water vapor pressure at 37°C in alveolar gas (Pb – P_{H_2O}), Thus:

$$[V_A \times kCO]/Pb^* = D_{LCO} \qquad (2)$$

$$\text{ml (STPD)} \times \text{min}^{-1}\ \text{mm Hg}^{-1} = \text{ml min}^{-1}\text{mm Hg}^{-1},$$

where $\dot{V}CO/Pb^*$ is the alveolar CO uptake per minute per mm Hg P_{CO}, which, as a conductance, defines the D_{LCO}. In pulmonary function reports D_{LCO} is divided by V_A with ml STPD exchanged for L BTPS:

$$D_{LCO}/V_{A\,L.BTPS} = [kCO/Pb^*]\cdot 1000/1.2 = KCO, \qquad (3)$$

where D_{LCO}/V_A and KCO have units of ml minute^{-1} mm Hg^{-1} L^{-1}, 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 D_{LCO}/V_A (= KCO) by three constant factors (Pb*, 1,000, and 1.2) and in its units. The ratios D_{LCO}/V_A (= KCO) to kCO and to kCO/Pb* (both constant except for minor variations in Pb) are given in the legend to Figure 1. Therefore, D_{LCO}/V_A (= 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 D_{LCO}/V_A.

WHAT DOES THE KCO SIGNIFY?

The previous section has shown that kCO (second^{-1} or minute^{-1}), kCO/Pb* (minute^{-1} · mm Hg^{-1}), and D_{LCO}/V_A (= KCO) (ml minute^{-1} mm Hg^{-1} L^{-1} 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 D_{LCO}/V_A, is the carbon monoxide diffusing capacity per unit alveolar volume, at the alveolar volume (V_A) 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 D_{LCO} corrected for lung volume, a concept that is wrong because D_{LCO} measured at a different volume, at a different level of V_A/V_{ATLC}, would yield a different value for D_{LCO}/V_A (= KCO) (*see* Figures 2 and 3). Paradoxically, D_{LCO}/V_A contains no information about the value of V_A, being a weighted mean value of the rate of CO uptake in the "accessible" V_A. 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 D_{LCO}/V_A.

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 T_{LCO}/V_A (~D_{LCO}/V_A) 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 D_{LCO}/V_A, 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 D_{LCO} falls and KCO rises (8, 11) (Figure 2). Expressed as a percentage of the value at predicted TLC (~$V_A$max), D_{LCO} at 50% $V_A$max is 79%, and KCO is 158% (8). This increased efficiency of alveolar uptake of carbon monoxide (KCO) at resting breathing volumes protects the D_{LCO} against undue volume dependence, that is, D_{LCO} is 80% of its TLC value at 50% $V_A$max 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 ($1/D_L = 1/D_M + 1/\theta \cdot Vc$), normalized to V_A:

$$V_A/D_{LCO} = 1/KCO = \ V_A/D_{MCO} + V_A/\theta_{bl_{CO}} \cdot Vc\ , \qquad (4)$$

where D_M is the membrane diffusing capacity; $\theta_{bl_{CO}}$ is the reaction rate of carbon monoxide with blood (minute^{-1} mm Hg^{-1}), adjusted to a standard hemoglobin (Hb) concentration; and Vc is the pulmonary capillary volume. With a decrease in alveolar expansion, the ratio V_A/D_M remains almost constant (13), so the fall in V_A/D_{LCO} (= rise in KCO) is caused by the decrease in V_A/Vc (= rise in Vc/V_A), with Vc remaining constant as V_A decreases (13). The change in Vc/V_A is consistent with the stability of pulmonary blood flow (approximately the cardiac output) during lung volume changes.

Changes on Exercise

During exercise, D_{LCO} (and KCO) rises at constant V_A (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

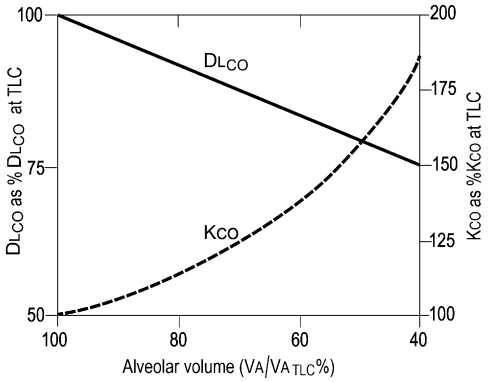

Figure 2. Effect of voluntary lung volume change on D_{LCO} and K_{CO}, plotted as a percentage of the value at full inflation (approximately TLC) against alveolar expansion expressed as alveolar volume as percent maximum ($V_{ATLC} \sim 93.5\%$ TLC). K_{CO}/K_{COTLC} at various values of V_A/V_{ATLC} was calculated from Equation 7 [$K_{CO}/K_{COTLC} = 0.43 + 0.57/(V_A/V_{ATLC})$], and $D_{LCO}/D_{LCO(TLC)}$ as $K_{CO}/K_{COTLC} \times V_A/V_{ATLC}$. *Definitions of abbreviations*: D_{LCO} = carbon monoxide diffusing capacity; K_{CO} = rate constant for carbon monoxide uptake per unit barometric pressure ($k_{CO}/Pb^* \sim D_{LCO}/V_A$); V_A = alveolar volume.

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

Variables That Can Be Controlled

Other factors that influence K_{CO} (but not V_A) are anemia and alveolar P_{O_2} because $\theta_{bl_{CO}}$ (*see* Equation 4) decreases as [Hb] falls or as alveolar P_{O_2} rises. A rise in the steady state P_{CO} in plasma (called the "back-pressure"), due to recent cigarette smoking or multiple preceding measurements of D_{LCO}, also lowers the D_{LCO}. Standard corrections for these three factors are available (9). The test gas includes 21–25% oxygen (depending on the helium concentration), so K_{CO} is usually measured at a normal alveolar $P_{A_{O_2}}$. K_{CO} is greater supine than erect, but clinical measurements are always made in the seated upright posture.

Reference Values

The predictions for D_{LCO} depend on age, sex, and height (17). Of the components of the D_{LCO}, V_A depends on sex and height but not on age, and, in adults, K_{CO} depends inversely on age and height but, in a review of the literature, hardly at all on sex (18). The highest values for K_{CO} have been found in boys and girls before the age of puberty (6), suggesting that the pulmonary capillary bed has developed earlier than alveolar volume. The decline in K_{CO} 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 K_{CO} 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 D_{LCO} and K_{CO}, and there is no consensus on the "best choice" (10). Thus, there is a need to acquire new reference values for D_{LCO} and for its components. The European Standardization Working Party (17) recommends that K_{CO} (predicted) be calculated as D_{LCO} (predicted)/TLC (predicted), from measurements made at different times and often in different places. Predicted values for K_{CO} would be better based on the two simultaneous measurements, that is, from D_{LCO} divided by single-breath "accessible" V_A rather than from two separate procedures (D_{LCO} and TLC).

Nomenclature and Units

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

CHANGES IN K_{CO} AND "ACCESSIBLE" V_A IN DISEASE

Clinical Causes of Decreases or Increases in K_{CO}

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

In relation to increases in K_{CO}, incomplete alveolar expansion, without compromise of alveolar structure, elevates K_{CO} by increasing V_c/V_A; a lesser increase in V_c/V_A is also largely responsible for the increase in K_{CO} 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 K_{CO} (and also D_{LCO}) in asthma is probably linked to better perfusion of the apices of the lungs (27), and this may explain, in part, the increase in K_{CO} in some obese patients, although a raised capillary volume and low D_M have been found (33), suggesting an element of pulmonary vascular 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 postpneumonectomy. This will increase the K_{CO} in the lung that remains. Corris and colleagues (30) established an empirical relationship in 28 patients for the increase in K_{CO} that occurred postpneumonectomy:

$$\Delta K_{CO}(\%\ \text{predicted}) = 0.4x + 2.1, \qquad (5)$$

where x was the percentage flow (%) to the resected lung, based on a preoperative radioisotope lung perfusion scan. K_{CO} postpneumonectomy was 110–131% predicted (mean K_{CO} preoperatively for both lungs averaged 98%); in the case in which flow to both lungs was equal preoperatively (x = 50%), Equation 5 predicts the K_{CO} 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 K_{CO} is the expected doubling of blood flow per unit volume in the remaining lung. This ΔK_{CO} is consistent with the 20% increase in K_{CO} when pulmonary blood flow in normal lungs increases from 5 L minute^{-1} at rest to 10 L minute^{-1} on moderate exercise (14). V_A after pneumonectomy averaged 50% of the preoperative value; thus, the remaining lung was expanded to its predicted TLC when the K_{CO} was measured

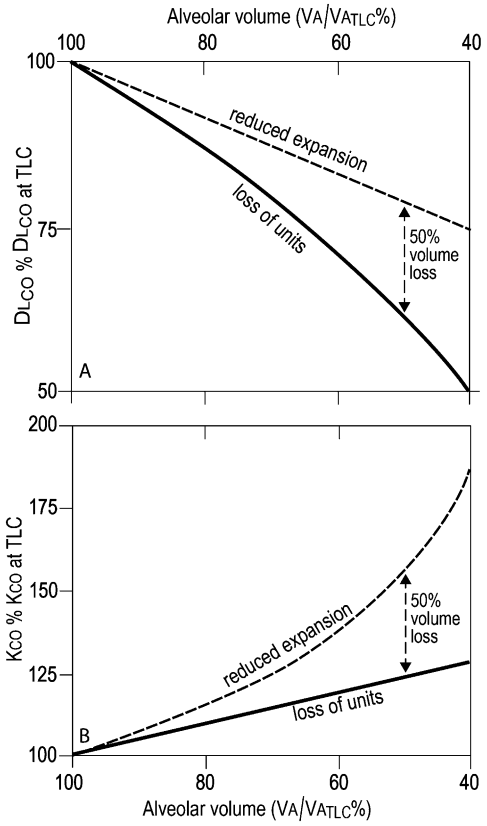

Figure 3. $D_{LCO}/D_{LCO\ (TLC)}$ and $K_{CO}/K_{CO_{TLC}}$ plotted against volume loss ($V_A/V_{A_{TLC}}$) from two causes: (*A*) reduced alveolar expansion (e.g., FRC vs. TLC), and (*B*) loss of units as in lobectomy or pneumonectomy. Reduced expansion calculations are from Figure 2. Loss of units calculated from Equation 5 (ΔK_{CO} [% predicted] = 0.4x + 2.1) on the assumption that "x" (% blood flow to lung to be resected) reflects percent lung volume to be resected; $D_{LCO}/D_{LCO\ (TLC)}$ calculated as $K_{CO}/K_{CO_{TLC}} \times V_A/V_{A_{TLC}}$. Note difference between $D_{LCO}/D_{LCO\ (TLC)}$ and $K_{CO}/K_{CO_{TLC}}$ for 50% volume loss according to the mechanism of the volume deficit.

postoperatively. Note that for a similar reduction of overall V_A to 50% predicted, but applied to both lungs by underexpansion (e.g., neuromuscular disease), the increase in K_{CO} at 50% $V_A/V_{A_{TLC}}$ is considerably greater (+58%: *see* Figure 2) than the +22% 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 D_{LCO} in Figure 3A and for K_{CO} in Figure 3B. The difference for K_{CO} in Figure 3B arises from different changes in the two components of the K_{CO} from the Roughton–Forster formula (Equation 4), V_A/D_M and V_A/Vc. With restricted alveolar expansion, D_M/V_A (inverse of V_A/D_M) and Vc (13) remain relatively constant; hence halving lung volume (to 50% $V_A/V_{A_{TLC}}$) will increase Vc/V_A to 200% and increase K_{CO} 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 K_{CO} to 120%; this arises from changes in both the D_M and Vc components of the Roughton–Forster equation: D_M/V_A increases to 133% and Vc/V_A to 141% of their resting values (14). The larger increase in Vc/V_A at 50% $V_A/V_{A_{TLC}}$ 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.

The increase in K_{CO} postpneumonectomy (30) (increased blood flow per unit volume) is a general phenomenon in many lung diseases in which blood flow is redistributed to less diseased areas with an increase in local flow and blood volume per unit alveolar volume; this redistribution may be the explanation for increases in K_{CO} seen occasionally in other conditions in which interstitial or vascular disease, in its early stages, is patchy, leading to blood flow diversion to the remaining normal lung. Thus, a normal or mildly elevated K_{CO} is seen in a proportion of cases with sickle cell disease (36), interstitial lung disease, and sarcoidosis (37).

Pulmonary hemorrhage (32), in which blood recently shed from capillaries takes up carbon monoxide, is the one example of a raised K_{CO} that is not linked to an increased rate of alveolar–capillary uptake. K_{CO} is more sensitive than D_{LCO} in detecting pulmonary hemorrhage (38) because of a small accompanying fall in V_A. In 39 patients, the maximal increase above baseline averaged 219% for K_{CO} but only 182% for D_{LCO}. In nine patients the peak rise in D_{LCO} was less than 50%, but the rise in K_{CO} above baseline always exceeded 50%.

Clinical Causes of a Low "Accessible" Alveolar Volume (V_A)

In the single-breath D_{LCO}, there are three distinct causes of a low V_A (as a percentage of $V_A$max predicted, ~93.5% ± 6.6

TABLE 1. PATHOPHYSIOLOGY AND CLINICAL EXAMPLES OF AN ABNORMAL K_{CO}

Low K_{CO}		High K_{CO}	
Mechanism	Clinical Examples	Mechanism	Clinical Examples
	With Normal or Near Normal V_A		
Microvascular destruction	Idiopathic pulmonary hypertension (19) Pulmonary vasculitis (20)	Increased pulmonary blood flow or redistribution	Left-to-right intracardiac shunts (26) Asthma (27)
Microvascular remodeling and dilation	Hepatopulmonary syndrome (21, 22) Pulmonary arteriovenous malformations (23)		
	With Reduced V_A		
Alveolar destruction	Emphysema (low "accessible" V_A)	Incomplete alveolar expansion to TLC	Inspiratory muscle weakness (28) Chest wall restriction (29) Poor cooperation or comprehension
Alveolar destruction	Diffuse interstitial lung disease with fibrosis	Increased pulmonary blood flow	Pneumonectomy (30)
Microvascular destruction	Bronchiolitis obliterans (24)	Microvascular congestion/dilation	Obesity (31)
Microvascular destruction	Chronic heart failure (severe) (25)	Alveolar hemorrhage	Anti-GBM disease (32), SLE

Definition of abbreviations: GBM = glomerular basement membrane; SLE = systemic lupus erythematosus.
Clinical examples are not an exhaustive list.

[1.0 SD] TLC) (Table 2) resulting in different values for the KCO (*see* Table 1):

1. Incomplete alveolar expansion (KCO > 120% predicted).
2. Loss of lung units (KCO 100–120% predicted). Besides pneumonectomy, localized destruction of lung ± 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 D_{LCO}

The D_{LCO} 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 D_{LCO} (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 D_{LCO} 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 airspaces, which remain (mostly) ventilated. This contrasts with Table 3, diagnosis C, in which the D_{LCO} 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 D_{LCO} in the presence of normal lung volumes without airflow obstruction suggests straightaway some pulmonary vascular pathology.

CURRENT VIEWS ON D_{LCO}/VA (= KCO)

In an earlier section (MEASUREMENT OF KCO AND VA: COMBINING VA AND KCO) we pointed out that current practice reports D_{LCO}/VA (= KCO) literally as D_{LCO} divided by VA with units ml minute^{-1} mm Hg^{-1} L^{-1}; this redundancy of units (the units of D_{LCO}/VA and KCO are essentially minute^{-1} mm Hg^{-1}, that is, kCO/Pb*; *see* Equation 2) has led to the idea that D_{LCO}/VA "adjusts" or "corrects" the D_{LCO} when the VA is lower than predicted. Because D_{LCO}/VA (= KCO) is not a constant function versus VA (Figures 2 and 3), several authors (40–42) have claimed that D_{LCO}/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 [= D_{LCO}] to share this flaw). The confusion arises from the substitution for KCO of its equivalent (D_{LCO}/VA), which gives the impression of a "volume correction." The ATS/ERS Task Force (9, 10) counsels caution in the use of the D_{LCO}/VA ratio, but nowhere is the connection made that the D_{LCO}/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 D_{LCO}/VA from being a "volume correction" for the D_{LCO} 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 D_{LCO}/VA as a correction factor for lung volume is misconceived, and reflects a misapprehension of the physiology. Hence, we believe the term D_{LCO}/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 D_{LCO}/VA (KCO). A typical relationship (data from 24 subjects) is as follows (8):

$$D_{LCO}/D_{LCO_{TLC}} = 0.58 + 0.42 \cdot (VA/VA_{TLC}), \qquad (6)$$

where $D_{LCO_{TLC}}$ and VA_{TLC} are expected values for D_{LCO} and VA at a normal predicted TLC. For a VA/VA_{TLC} ratio of 0.5,

TABLE 2. CAUSES OF LOW VA AND TYPICAL KCO FINDINGS

Pathophysiology	Clinical Examples	KCO as % KCO at Predicted TLC
	Restrictive (Reduced TLC)	
Incomplete alveolar expansion	Inspiratory muscle weakness Chest wall, pleural restriction Inadequate inspiration to TLC	120–140 (28)
Loss of units "localized"	Pneumonectomy, local destructive or infiltrative pathology	100–120 (30)
Loss of units "diffuse"	Interstitial lung disease with fibrosis	<80
	Obstructive (Normal/High TLC)	
Poor mixing + normal alveolar function	Asthma	100–120 (27)
Poor mixing + localized loss of units	Bronchiectasis	90–100[†]
Poor mixing + some alveolar loss/disorganization	Bronchiolitis obliterans	70–100 (24)
Poor mixing + diffuse alveolar disorganization	COPD (chronic bronchitis and emphysema)	40–90

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; KCO = rate constant for carbon monoxide uptake per unit barometric pressure (kCO/Pb* ~ D_{LCO}/VA); VA = alveolar volume.

[†] D. Cramer, Royal Brompton Hospital, London, UK, personal communication.

TABLE 3. VARIOUS K_{CO}–V_A PATTERNS AND PATHOLOGIES, BUT SIMILAR D_{LCO}

Diagnosis	D_{LCO} % Predicted	K_{CO} % Predicted	V_A % Predicted	Comment
A. Inspiratory muscle weakness	59	120	50	Lack of alveolar expansion
B. Pneumonectomy	58	111	51	Localized loss of lung units
C. Diffuse interstitial lung disease	54	84	66	Alveolar capillary damage (±loss of units)
D. Emphysema	54	59	91	Alveolar capillary damage
E. Idiopathic pulmonary hypertension	56	58	96	Microvascular damage

Definition of abbreviations: D_{LCO} = single-breath diffusing capacity for carbon monoxide; K_{CO} = rate constant for carbon monoxide uptake per unit barometric pressure ($k_{CO}/Pb^* \sim D_{LCO}/V_A$); V_A = alveolar volume.

D_{LCO} would be multiplied by 1.26 to adjust for the volume reduction. The relationship for K_{CO} was

$$K_{CO}/K_{COTLC} = 0.43 + 0.57/(V_A/V_{ATLC}) \quad (7)$$

Thus, K_{CO} would be adjusted down at 0.5 V_A/V_{ATLC} 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 D_{LCO} and K_{CO} (as a percentage of the predicted value), with K_{CO} (%) exceeding D_{LCO} (%) by up to 50%. After adjustment of K_{CO} for a low V_A, D_{LCO} and K_{CO} tended to converge. Using a similar approach, Frans and colleagues (43) reported convergence of D_{LCO} and K_{CO} values after adjustment of both for the low V_A in diffuse interstitial lung disease. Basically, these "corrections" return a high K_{CO} in extrapulmonary restriction to values in the 90–100% predicted range, and in interstitial lung disease and sarcoidosis they adjust the K_{CO} down from 75–105% predicted to 50–75% predicted, more in line with the uncorrected D_{LCO}. The authors (8, 43) argue that "normal" values for D_{LCO}/V_A (unadjusted) in interstitial lung disease give the clinician a "false" impression that the gas-exchanging part of the lung is "healthy." Stam and colleagues (44) studied patients who developed alveolar injury after bleomycin treatment. After bleomycin, the K_{CO} reduction was greater (by up to 11%) if its value was referenced to the K_{CO} at the actual lung volume rather than the predicted TLC. They concluded, like others (8, 43), that the volume restriction had "misleadingly" increased the K_{CO}.

The flaw in the argument is that alveolar restriction by underexpansion is only one of at least three mechanisms causing a low V_A (Table 2). For example, it is unlikely that the majority of the alveolar units contributing to the K_{CO} in interstitial lung disease, pneumonectomy, or airflow obstruction from various causes are "underexpanded." Hughes and Pride (2) presented corrections for a high K_{CO} and low V_A using two models (alveolar underexpansion, and increased pulmonary blood flow; based on Equation 5; *see* their Table 3), but this is hardly a practical solution for the clinician, and does not address the question of low V_A caused by poor gas mixing.

It is not unreasonable to seek an interpretation of, or correction for, the D_{LCO} when V_A is reduced. For example, it would be legitimate to correct D_{LCO} and K_{CO}, using Equations 6 and 7, for underexpansion of the lung during breath holding (due to extrapulmonary restriction or technical artifact) provided that alveolar deflation was the sole cause of the low V_A. Our contention is that any "correction" of the D_{LCO} for volume (V_A) must take into account the reason for the volume deficit—for 50% volume loss (V_A = 0.5 V_{ATLC}) D_{LCO}/V_A (= K_{CO}) will be significantly greater in extrapulmonary restriction than after a pneumonectomy or maldistribution of inspired gas as in bullous emphysema. There is no easy solution to this problem. There is no "correct" way in which the rate constant ($k_{CO} \sim k_{CO}/Pb^* \sim K_{CO}$) can be properly adjusted for all the causes of low alveolar volume. A grasp of physiological principles (*see* DETERMINANTS OF K_{CO} IN NORMAL SUBJECTS) is the best way to understand the clinical significance of D_{LCO}, K_{CO}, and V_A.

THE DIFFUSING CAPACITY FOR NITRIC OXIDE (D_{LNO})

In the last two decades, the measurement of pulmonary diffusing capacity using nitric oxide (D_{LNO}) has been introduced (45, 46). D_{LNO} is 4 to 4.5 times greater than D_{LCO}, partly because the physical diffusivity of nitric oxide is about twice that of carbon monoxide, and partly because red cell resistance to nitric oxide uptake is less than that to carbon monoxide (47) owing mostly to the much faster combination (by 280-fold) of nitric oxide with hemoglobin (Hb). Unlike D_{LCO}, D_{LNO} is P_{O_2} independent (48). The low red cell resistance suggests that D_{LNO} 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 (D_M). D_{MNO} is related to the better known D_{MCO} by α (= 1.97), the ratio of the physical diffusivities of nitric oxide and carbon monoxide in plasma, that is, $D_{MNO}/\alpha = D_{MCO}$.

Guenard and colleagues (45) measured D_{LNO} and D_{LCO} simultaneously by the classical single-breath technique. Assuming $D_{MNO}/\alpha = D_{MCO}$, they showed that the Roughton–Forster formulation ($1/D_{LCO} = 1/D_{MCO} + 1/\theta_{bl_{CO}}Vc$) could be rearranged:

$$1/Vc = \theta_{bl_{CO}}(1/D_{LCO} - \alpha/D_{LNO}) \quad (8)$$

Reasonable values of D_{MCO} and Vc were obtained in normal subjects (45).

Although, for clinical interpretation, D_{LNO} may be regarded as a surrogate for the membrane diffusing capacity (D_M), the notion that $\theta_{bl_{NO}}$ is infinite has been called into question. Measurements of D_{LNO} before and after experimentally induced hemolysis (49) and after blood substitution, in anesthetized dogs, with cell-free heme-based oxyglobin (50), suggest that D_{LNO} is not entirely "red cell independent." After oxyglobin exchange transfusion, in the red cell–free state, D_{LNO} increased 1.5 times (D_{LCO} did not change), which suggests that D_{MNO} is 1.5 times D_{LNO} rather than its equivalent. It was suggested previously that D_{LNO} might be a surrogate for $D_{L_{O_2}}$ (51).

THE D_{LNO}/D_{LCO} RATIO

Because of reservations about the relevance of *in vitro* measurements of $\theta_{bl_{CO}}$ and $\theta_{bl_{NO}}$ to the *in vivo* situation (49, 50), interest is shifting from estimates of D_M and Vc toward the D_{LNO}/D_{LCO} ratio. Assuming, for clinical purposes, that $\theta_{bl_{NO}}$ is infinite so that $D_{LNO} = D_{MNO} = D_{MCO}\cdot\alpha$, and from the Roughton–Forster equation for carbon monoxide (12):

$$D_{LNO}/D_{LCO} = \alpha(1 + D_{MCO}/\theta_{bl_{CO}}\cdot Vc) \quad (9)$$

Thus, the D_{LNO}/D_{LCO} ratio is weighted toward the D_M/Vc ratio and α (the NO/CO physical solubility ratio). It is also equivalent

to the K_{NO}/K_{CO} ratio because $D_L = K \times V_A$, and V_A is common to $D_{L_{NO}}$ and $D_{L_{CO}}$ when measured simultaneously by the standard single-breath technique with inhalation of nitric oxide and carbon monoxide. Measurements of the $D_{L_{NO}}/D_{L_{CO}}$ ratio have been performed in normal subjects, at rest and during exercise (53–55), and over a range of lung volumes (56, 57). The $D_{L_{NO}}/D_{L_{CO}}$ ratio has been studied in several clinical situations. For example, the $D_{L_{NO}}/D_{L_{CO}}$ 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/V_A is reduced more than D_M/V_A. In contrast, the $D_{L_{NO}}/D_{L_{CO}}$ ratio is decreased at FRC versus TLC (56), the explanation being that $D_{L_{NO}}$ is more sensitive to alveolar underexpansion than $D_{L_{CO}}$. For example, from $V_{A_{TLC}}$ to $V_{A_{50\%\ TLC}}$ the $D_{L_{NO}}$ declines by 43% versus 29% for $D_{L_{CO}}$ (56). The reason is that the fall in $D_{L_{CO}}$ is buffered by an increase in K_{CO} (+35%) whereas K_{NO} (being less influenced by the rise in Vc/V_A) increases by only 10% (56). Thus, the $D_{L_{NO}}/D_{L_{CO}}$ ratio could become a marker for extrapulmonary restriction.

The $D_{L_{NO}}/D_{L_{CO}}$ ratio gives some insights into the components (D_M and Vc) of the Roughton–Forster equation in a single maneuver without the two-step approach with carbon monoxide at different alveolar P_{O_2} as well as by-passing $\theta_{bl_{CO}}$, the value of which is somewhat controversial (51, 52). Experience to date with D_M and Vc partitioning has been disappointing because commonly both change equally (the only notable example of discordance [$D_M\downarrow$, $Vc\uparrow$] being chronic heart failure [34, 35]); thus, we would expect a low $D_{L_{NO}}/D_{L_{CO}}$ ratio in chronic heart failure, at least in the early stages. It is also possible that by factoring out V_A, the $D_{L_{NO}}/D_{L_{CO}}$ ratio (= K_{NO}/K_{CO}) may provide additional insight into other respiratory diseases.

CONCLUSIONS

The single-breath $D_{L_{CO}}$ is, physiologically, the product of two simultaneous measurements: the rate of carbon monoxide uptake from alveolar gas to pulmonary capillary blood (k_{CO}), reexpressed per mm Hg alveolar dry gas pressure (Pb*) as k_{CO}/Pb^*, and the "accessible" alveolar volume (V_A), which approaches, in normal subjects, TLC. k_{CO}/Pb^* is linked mathematically to $D_{L_{CO}}/V_A$ (= K_{CO}). The term $D_{L_{CO}}/V_A$ is misleading because, as k_{CO}/Pb^*, it reflects the rate of alveolar uptake of CO.

The common causes of a low V_A 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" $D_{L_{CO}}$ for all the causes of a low V_A, and the use of the term $D_{L_{CO}}/V_A$ should be replaced by its alternative, K_{CO}.

Clinical interpretation of a low $D_{L_{CO}}$ (as a percentage of the predicted value) stems from inspection of the components of the $D_{L_{CO}}$ (K_{CO} and V_A) and knowledge of physiological principles. From a consideration of the K_{CO} and V_A (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 ($D_{L_{NO}}$) may enable us to focus on alveolar structure differently from the $D_{L_{CO}}$. The $D_{L_{NO}}/D_{L_{CO}}$ ratio may be a surrogate for the D_M/Vc ratio and $D_{L_{NO}}$ may provide information on total barrier (tissue and blood) thickness, largely independent of any chemical resistance introduced by the presence of hemoglobin.

Author disclosures are available with the text of this article at www.atsjournals.org.

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