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PERSPECTIVE

In defence of the carbon monoxide transfer coefficient *K*CO (*T*L/*V*A)

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In defence of the carbon monoxide transfer coefficient KCO (TL/VA). *J.M.B.Hughes, N.B.Pride.* ©*ERS Journals Ltd 2001.*

ABSTRACT: The carbon monoxide transfer factor (*T*L,CO) is the product of the two primary measurements during breath-holding, the CO transfer coefficient (*K*CO) and the alveolar volume (*V*A). *K*CO is essentially the rate constant for alveolar CO uptake (Krogh's *k*CO), and in healthy subjects, increases when *V*A is reduced by submaximal inflation, or when pulmonary blood flow increases. Recently, new reference values were proposed for clinical use which included the observed *V*A at full inflation; this was claimed to "eliminate the need for *K*CO".

In this commentary, some mechanisms *e.g.* respiratory muscle weakness, lung resection, diffuse alveolar damage and airflow obstruction, which decrease or increase total lung capacity (TLC) are reviewed.

Even when alveolar structure and function are normal, the change in *K*CO at a given *V*A varies according to the underlying pathophysiological mechanism. The advantages and disadvantages of normalizing *K*CO and *T*L,CO to predisease predicted TLC or to the patient's actual *V*A (using lack of expansion or loss of alveolar units models) are considered.

Examination of carbon monoxide transfer coefficient and alveolar volume separately provides information on disease pathophysiology which cannot be obtained from their product, the carbon monoxide transfer factor.

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A few years ago, a paper in the *European Respiratory Journal* [1] concluded that: ". . . the use of *T*L/*V*A (the carbon monoxide (CO) transfer coefficient) cannot be justified on scientific grounds". Apart from one letter of disagreement [2], this view that *T*L/*V*A (or *K*CO) is a redundant and misleading measurement has not been challenged. This is surprising because measurements of *T*L/*V*A have continued to be published in respiratory journals.

The single breath method for measuring CO uptake by the lung, which is used world-wide, was introduced by KROGH [3] in 1915; this measurement was termed diffusion constant. Subsequently the diffusion constant for CO was renamed the diffusing capacity (*D*L,CO) or the transfer factor (*T*L,CO), with the uptake being measured at total lung capacity (TLC). KROGH [3] pointed out that *T*L,CO was the product of two separate measurements, which potentially varied widely (and independently), the rate constant for CO removal from alveolar gas (called the permeability factor (*k*CO)) and the alveolar volume (*V*A).

*k*CO is measured as the exponential decay in fractional concentration of CO over a period of breath-holding (BHT):

$$k\mathrm{CO} = (\log_e[\mathrm{CO}_0/\mathrm{CO}_t])/\mathrm{BHT} \qquad (1)$$

where CO_0 and CO_t are the alveolar CO concentrations at the start and finish of the breath-holding period. The units of *k*CO are s^{-1} or min^{-1}.

The total CO transfer of the lung is calculated as:

$$T\mathrm{L,CO} = [k\mathrm{CO} \times V\mathrm{A}\ \ \mathrm{STPD}]/[P\mathrm{B} - P_{\mathrm{H_2O}}] \qquad (2)$$

where *P*B and *P*H2O are the barometric pressure and the water vapour pressure (at 37°C) which standardize for the driving pressure for CO uptake, *i.e.*the pressure of CO in the alveoli (*P*A,CO). *V*A is the alveolar volume measured at standard temperature and pressure, dry (STPD).

In modern usage, M. Krogh's *k*CO is rarely employed; instead, the carbon monoxide transfer coefficient is substituted, whose units of $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$ (at body temperature and ambient pressure, and saturated with water vapour (BTPS)) give the appearance of being a ratio, an impression enhanced by its terminology (*T*L/*V*A or *D*L/*V*A). In fact, *k*CO converts to the carbon monoxide transfer coefficient by dividing by the STPD to BTPS conversion (1.2), by a L to mmol change (1,000/22.4) (if in SI units), and by the barometric pressure term (*P*B - P_{H_2O}). In SI units, *k*CO (min^{-1}) converts to *K*CO (*T*L/*V*A) by dividing by 2.56.

The objection of CHINN *et al.* [1] to the use of *T*L/*V*A is that "VA was the largest single contributor to the variance in *T*L/*V*A"; unfortunately, this gives the

misleading impression that *T*L/*V*A is derived from *T*L,CO by dividing *T*L by *V*A, whereas *T*L/*V*A and *V*A are the two primary measurements used to obtain *T*L,CO. An unambiguous way to rephrase this objection would be to say that the rate constant for CO uptake varies with *V*A, as shown (within an individual) by KROGH [3] in 1915, and confirmed by all subsequent authors.

The variation in *K*CO with *V*A in normal subjects has been investigated extensively since 1959 [4]; in 1994, STAM *et al.* [5] suggested that in restrictive lung disease values of TL,CO and *K*CO should be compared with reference values both at the patient's predicted total lung capacity (TLC) and at the lung volume equal to the patient's actual TLC; this suggestion has been endorsed subsequently [1, 6, 7]. The novelty in the approach of CHINN *et al.* [1] rests on the development of reference values for *T*L,CO and *K*CO, which include a term for *V*A (at TLC) as well as a height term, *i.e.* they take into account variation in TLC at a standard height. Extrapolating from this, they suggest that their reference equations may be used to interpret *T*L,CO when *V*A is reduced or increased in disease, " . . . and eliminate the need for the carbon monoxide transfer coefficient". On the contrary, the present authors argue that both primary measurements (*K*CO and *V*A) should always be examined, especially in disease.

Determinants of carbon monoxide transfer coefficient in normal subjects

Within individuals

In a healthy subject, the degree of lung inflation and the pulmonary capillary volume are probably the major determinants of *T*L,CO and *K*CO. Figure 1 shows that *K*CO and *T*L,CO are functions of alveolar expansion [5], cardiac output [8], and haemoglobin concentration [9]. The extensive studies of STAM *et al.* [5] have emphasized that with a reduction in alveolar expansion down to 50% TLC the rise of *K*CO is linear, although earlier studies [4, 10] found a steeper rise at $V_A < 50\%\ V_{A,max}$. Despite this increase in *K*CO, the product $K_{CO} \times V_A$ *(i.e* *T*L,CO) falls as *V*A declines. On exercise, *K*CO (and *T*L,CO) increases from its value at rest (cardiac output 5 L·min^{-1}) by ~20% per 5 L min^{-1} increase in blood flow.

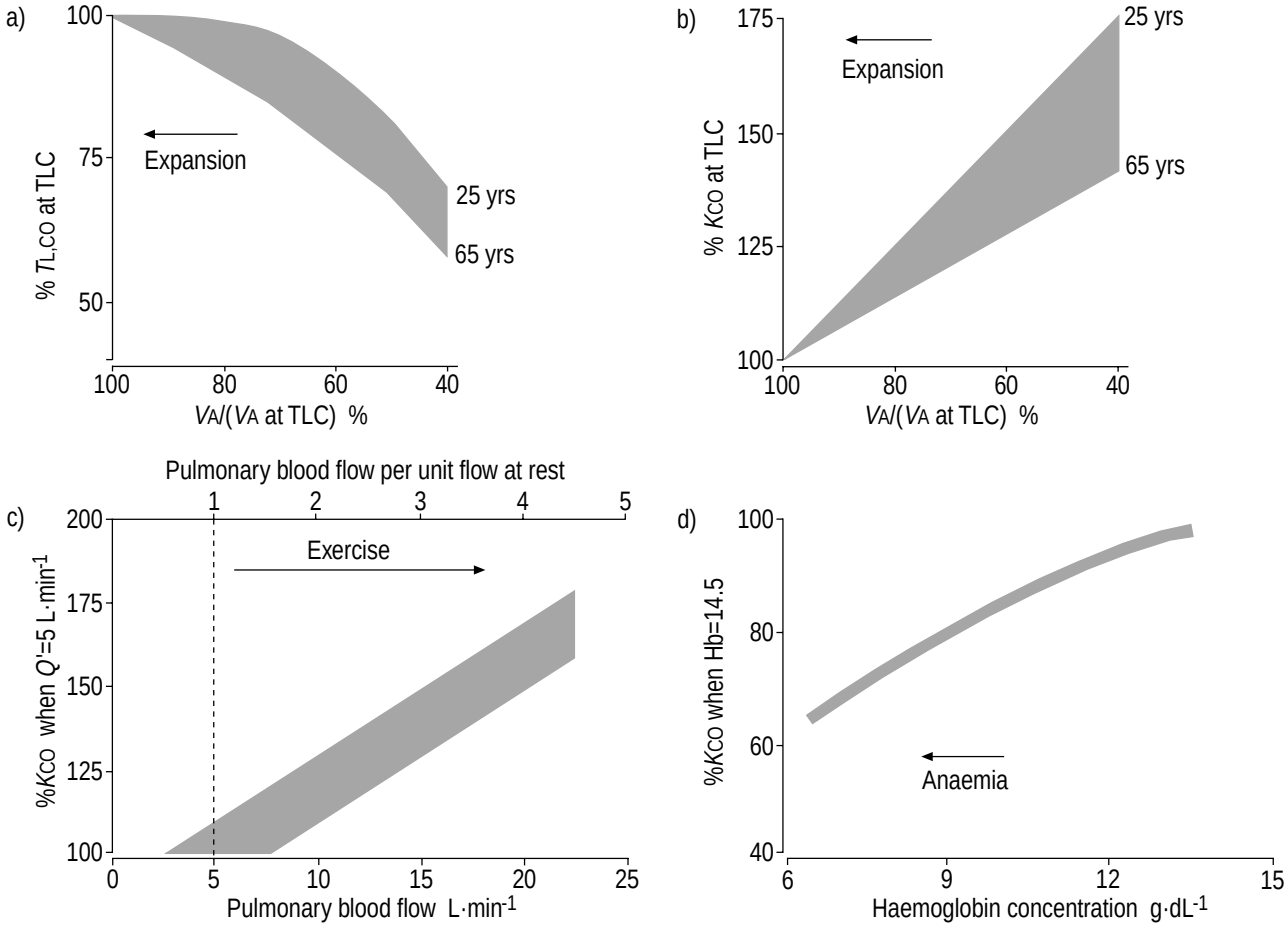

Fig. 1. – In a) the transfer factor (*T*L,CO) and b) carbon monoxide transfer coefficient (*K*CO) are plotted against alveolar volume (*V*A) as per cent of the *V*A value at total lung capacity (TLC), at different levels of alveolar expansion (indicated by arrow). There is a systematic change with increasing age. (Data replotted from [5].) In c) and d) *K*CO (normalized as indicated, and measured at TLC) is plotted against c) pulmonary blood flow at rest (- - - -) and on exercise, data from [8]; and d) against haemoglobin concentration (data from [9]). *T*L,CO would behave similarly.

The physiological explanation for these changes is given in the Roughton-Forster equation [11], corrected for V_A:

$$V_A/T_{L,CO} = V_A/D_m + V_A/\theta_{Hb}Q_c \quad (3)$$

where Dm is the membrane diffusing capacity (mmol·min^{-1}·kPa^{-1}), θ is the reaction rate of CO with haemoglobin adjusted to a standard haemoglobin (Hb) concentration (mmol·min^{-1}·kPa^{-1}·L^{-1}) and Q_c is the pulmonary capillary volume (L); the units of all three terms are mmol^{-1}·min·kPa·L^{-1}.

As the expansion of the lung diminishes, D_m in absolute terms falls, but Q_c does not change in any systematic way [12, 13]. Therefore, the fall in $T_{L,CO}$ (fig. 1a) is dominated by the fall in D_m. K_{CO}, on the other hand, is dependent on the ratios, D_m/V_A and Q_c/V_A. In the sitting position [12, 13], the fall in D_m is almost proportional to the fall in V_A, so the rise in K_{CO} as V_A falls (fig. 1b) is dominated by the rise in Q_c/V_A.

Several other physiological factors influence K_{CO} at a given V_A. As cardiac output rises on exercise (fig. 1c), Q_c/V_A increases by capillary distension and recruitment; D_m/V_A also increases slightly because vascular distension expands the alveolar surface available for gas exchange. In contrast, anaemia, by reducing θ/V_A will reduce K_{CO} (fig. 1d) and $T_{L,CO}$ similarly. A low alveolar oxygen tension (P_{a,O_2}), as occurs at altitude, will increase K_{CO} by increasing θ/V_A [14], and any accompanying polycythaemia will enhance this.

Technical factors can influence the value of K_{CO} such as the speed of the initial inspiration (it should be rapid) and the method used to measure the BHT. As shown in fig. 1a and b, inadequate inflation of the lungs to $V_{A,max}$ in the single breath test, will result in a low $T_{L,CO}$ and a high K_{CO}. For clinical purposes, the recommendation [15–17] is that the preceding inspired volume from residual volume (RV) should be at least 90% of the subject's vital capacity (VC) so that, with normal gas mixing, the $T_{L,CO}$ and K_{CO} measurements are made at $\geqslant$90% of actual TLC [18]. Because gas mixing is not quite complete in the 10 s BHT, $V_{A,max}$ in normal subjects is on average 94±7% of TLC, or 0.1–0.6 L less in absolute terms [18].

Between individuals

After standardization for age, height and sex, CHINN *et al.* [1] found a very similar relation between $T_{L,CO}$ and V_A measured at full inflation in their population study (*i.e.* an inverse relationship between K_{CO} and V_A) to that found with submaximal inflation in an individual. Therefore, they propose an additional V_A term to improve the relatively inaccurate predictions of reference values of $T_{L,CO}$ and K_{CO}. They support their own population study by reviewing the mean values of predicted $T_{L,CO}$ and V_A from nine published studies of reference values and, at least in males, find these share a similar relation of $T_{L,CO}$ to V_A. Unfortunately, the ratio V_A/TLC was not available in any of these studies, but using TLC predicted (TLC_{pred}) from mean age and height, eight studies had $V_A/TLC_{pred} \geqslant 0.90$ while the remaining study [19], which has a disproportionate influence on the slope, had V_A/TLC_{pred} of only 0.77. Therefore, further studies, which include individual measurement of V_A/TLC, are needed to establish the presence and size of any effect of differences in TLC at a given height on values of K_{CO} and $T_{L,CO}$ in a healthy population.

Effects of altered alveolar volume on transfer factor for carbon monoxide and transfer coefficient in respiratory disease

Reduction in alveolar volume and total lung capacity

As discussed above, STAM *et al.* [5] suggested that when TLC is reduced by disease, $T_{L,CO}$ values should be compared with reference values based on the observed V_A, but they cautioned that this assumes that "the effect of decreasing lung volume by disease has the same effect on T_L/V_A as the voluntary reduction in lung volume in healthy volunteers". Some of the different mechanisms of reductions in V_A at TLC are outlined in table 1, and will be reviewed to emphasize the weaknesses of this assumption.

Respiratory muscle weakness

The most obvious simulation of voluntary reduction in $V_{A,max}$ (table 1, lack of lung expansion mechanism),

Table 1. – Different mechanisms reducing single-breath alveolar volume (V_A) in respiratory disease

Disease	Mechanisms	Prototype	Other examples with comments
Restrictive disease with a small TLC and normal V_A/TLC ratio	Lack of lung expansion: lung structure normal	Acute inspiratory muscle weakness	Chest wall disease and pleural disease, but lack of expansion is usually nonuniform
	Loss of units: remaining lung structure normal	Pneumonectomy	Local alveolar infiltrate or collapse, consolidation or local destruction
	Diffuse alveolar damage	Fibrosing alveolitis	Pulmonary oedema, congestive heart failure, mitral stenosis, bleomycin lung, Wegener's granulomatosis. In all these conditions, severity of alveolar involvement varies and some normal alveoli survive and contribute to CO uptake
Obstructive disease with normal or increased TLC	Sampled V_A < TLC due to incomplete mixing during breath-holding	Emphysema	Incomplete mixing may be associated with alveolar destruction, space-occupying lesions (bullae) or normal alveolar structure (asthma)

TLC: total lung capacity.

occurs when acute inspiratory muscle weakness prevents the achievement of a "normal" TLC; in this case, the lack of inflation of the lung can be expected to be relatively uniform and associated with a reduced lung elastic recoil pressure (P_L) at $V_{A,max}$, and preservation of a similar distribution of cardiac output and pulmonary capillary volume as in normals. Thus $T_{L,CO}$ should fall and *K*CO should rise from the conventional TLC reference values as predicted in fig. 1a and b. In six patients with severe isolated diaphragm weakness [20], the mean $T_{L,CO}$ was 65% pred (range 44–78) and the mean *K*CO was 128% pred (range 101–167) at 60% of predicted maximum V_A; a $T_{L,CO}$ of 80–85% and a *K*CO of 130–140% would have been predicted on a reduced V_A expansion model (fig. 1). A possible explanation for the lower $T_{L,CO}$ and *K*CO than expected is secondary atelectasis; the remaining aerated lung units would then be more expanded than indicated by the actual level of V_A, and have a lower *K*CO.

Loss of alveolar units

The physiological situation with a reduction in V_A and TLC (table 1, loss of units mechanism) from lung resection, *e.g.* pneumonectomy, is completely different. First, P_L and the dimensions of the remaining airspaces are normal or even increased [21] at full inflation. Secondly, total pulmonary blood flow probably remains at preresection levels so that, depending on the flow-partitioning preoperatively, flow to the remaining lung per unit volume will increase up to two-fold (as if cardiac output had doubled from 5 to 10 L min^{-1}), a situation analogous to the *K*CO *versus* cardiac output plot in fig. 1c. This relationship between *K*CO and pulmonary blood flow can be transposed into a plot of *K*CO against loss of alveolar units (as $V_A/V_{A,max}$ %), where 50% $V_{A,max}$ is equivalent to the *K*CO for the whole lung at double the resting cardiac output (10 L·min^{-1}) and 33% $V_{A,max}$ is equivalent to a three-fold increase of blood flow per unit volume (fig. 2b). The $T_{L,CO}$ which results from these opposing changes of *K*CO and V_A is also shown (fig. 2a).

Preservation of Q_c is the reason why, for a given V_A, $T_{L,CO}$ and *K*CO in figure 2 are higher in the incomplete alveolar expansion situation than for loss of alveolar units. At 50% $V_{A,max}$, for loss of units, the data of HSIA *et al.* [8], expressing the values for one lung at twice resting pulmonary blood flow as per cent of both lungs at resting flow, would predict a D_m of 58% and a Q_c of 67%. On the other hand, with voluntary reduction to 50% $V_{A,max}$, D_m (as % D_m at $V_{A,max}$) would also be 58% but Q_c would be 100% [12]. Both models presuppose that the alveolar units of the V_A have normal function; deviations from the expected values will occur when this is not the case.

From the data in 28 patients CORRIS *et al.* [22] established an empirical relationship for the increase in *K*CO post-pneumonectomy:

$$\Delta K_{CO}\ (\%\text{pred}) = 0.41x + 2.1 \qquad (4)$$

where x is the percentage flow to the resected lung preoperatively, based on a radioisotope lung perfusion scan. For equal flow to both lungs before pneumonectomy (x=50%), they found that post-pneumonectomy *K*CO was 110–131% for a mean *K*CO preoperatively of 98%. Since $V_{A,max}$ after pneumonectomy averaged 50% of pred TLC [22], the loss of units model (fig. 2b) implies a doubling of pulmonary blood flow per unit volume with a *K*CO in the range 117–125% pred, which is similar to the results of CORRIS *et al.* [22]. The reduced alveolar expansion model, conversely, would predict a much higher *K*CO of 145–155% (fig. 2b).

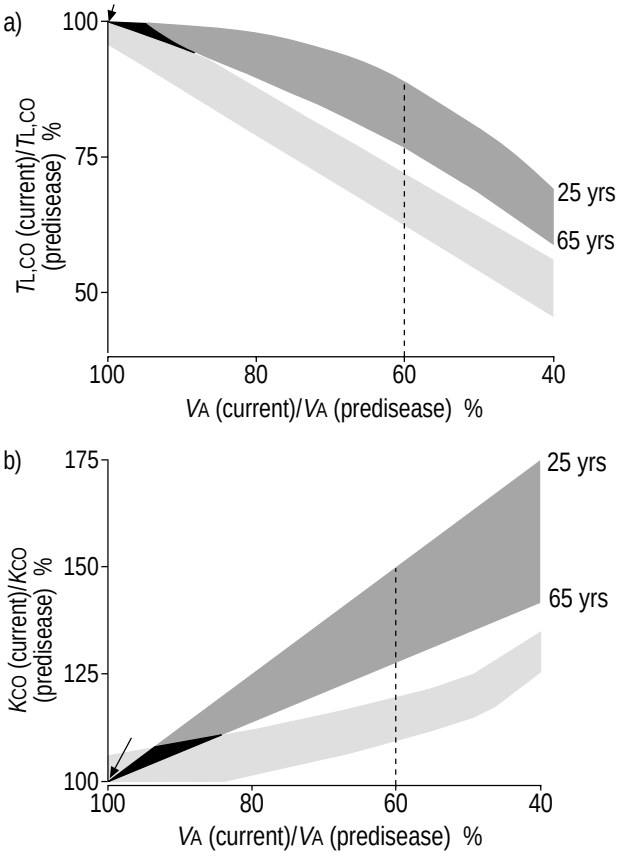

Fig. 2. – Predicted changes in a) the transfer factor ($T_{L,CO}$) and b) carbon monoxide transfer coefficient (*K*CO) at full inflation when total lung capacity (TLC) is reduced by disease. $T_{L,CO}$ and *K*CO are plotted against alveolar volume (V_A) as a fraction of V_A at predisease TLC for two different causes of V_A reduction, incomplete alveolar expansion (■), and loss of alveolar units. Incomplete expansion follows figure 1a and 1b. The loss of units plot (□) is derived from figure 1c by transposing the *K*CO ($T_{L,CO}$ is similar) at twice pulmonary blood flow at rest to *K*CO at 50% $V_{A,max}$, and the *K*CO at 1.5 times blood flow increase to 66% $V_{A,max}$, *etc*. The dashed line indicates different benchmarks for a V_A of 60% of the predisease value against which a patient's *K*CO or $T_{L,CO}$ at that V_A could be compared to the standard reference point (shown by an arrow). See text for explanation.

Diffuse alveolar damage

In the preceding two examples, the structure and expansion of the lung remains uniform, whereas in chronic interstitial lung disease (table 1, diffuse alveolar damage mechanism) the structural and functional changes are characteristically nonuniform. In the

most abnormal ventilated alveolar units, volume, D_m and Q_c are reduced and K_{CO} is low. On the other hand, there may be some redistribution of blood flow to the least abnormal alveolar units whose K_{CO} may be increased (fig. 2b, loss of units). Depending on the overall weighting, the whole lung K_{CO} (using standard reference values) may be low or even normal. In fibrosing alveolitis, for example, a K_{CO} of 100% pred at a low V_A implies from fig. 2b some degree of diffuse alveolar damage.

STAM *et al.* [7] have recently studied the pre- and postdisease dependence of K_{CO} and $T_{L,CO}$ on V_A in a group of young males without previous pulmonary disease, some of whom developed changes in the lungs, accompanied by modest reductions in $T_{L,CO}$ and K_{CO}, when treated with bleomycin for a germ cell tumour. In these males (and in one 11-yr-old female with interstitial lung disease [23]), the absolute change in $T_{L,CO}$ and K_{CO} with change in V_A (L) was similar before and after disease developed, supporting their contention that the extent of disease was assessed more correctly, and appeared greater, if values of $T_{L,CO}$ and K_{CO} were compared to reference values for the actual TLC rather than to values for the predicted (predisease) TLC. While this may be justified in the unique circumstances of their study, usually predisease TLC is unknown.

Airflow obstruction

TLC is normal or increased in most patients and the low single-breath V_A ($V_{A,SB}$) in airflow obstruction (table 1, V_A < TLC due to incomplete mixing mechanism) is caused by incomplete mixing, within the BHT, between the inspired He-CO gas mixture and the RV in the lungs. Without airflow obstruction, the V_A at full inflation should be ~90–95% of the TLC [18], but, with airflow obstruction, $V_{A,SB}$/TLC is often <80%. In the derivation of $T_{L,CO}$, the volume (V_A) term could either be the true TLC (minus the anatomic dead space), as originally proposed by OGILVIE *et al.* [24] (this would give a maximum or upper-bound value for $T_{L,CO}$) or $V_{A,SB}$ (which would give a minimum or lower bound $T_{L,CO}$). The European Respiratory Society guidelines recommend the use of TLC, but most pulmonary function laboratories prefer to use $V_{A,SB}$ because no extra measurement is required. The higher bound value for $T_{L,CO}$ (equivalent to $K_{CO} \times$ TLC) includes the poorly ventilated units by assigning them a K_{CO} equal to that of the well ventilated units (equivalent to measured K_{CO}). The lower bound value for $T_{L,CO}$ ($K_{CO} \times V_{A,SB}$) excludes the poorly ventilated units (equivalent to TLC - V_A difference). Nevertheless, asthma apart, it is probable that the poorly ventilated units will be more affected by the disease process, so that the true gas-exchanging potential will lie closer to the lower bound $T_{L,CO}$ value.

The use of the carbon monoxide transfer coefficient in clinical practice

K_{CO} is an index of alveolar gas exchange efficiency in terms of available surface area (D_m/V_A) and vascular density (Q_c/V_A). Disease processes, which reduce alveolar surface and capillary density (emphysema, fibrosis), or which, more selectively, lead to loss of the microvasculature (vasculitis, intrapulmonary shunting, heart failure) reduce the K_{CO} (table 2) and $T_{L,CO}$, often severely. In practice, by using the standard reference values for $T_{L,CO}$ at the predicted TLC, the upper or lower-bound values of $T_{L,CO}$ and K_{CO} (% pred) have shown good correlations in emphysema with anatomical measurements of airspace surface area per unit lung volume on subsequently resected lobes [30–32]. In addition, the K_{CO} correlates with X-ray computed tomography (CT) scan hypodensity *in vivo* [32]. In the assessment of patients with bullous emphysema for lung surgery, the K_{CO} is a guide to the physiological status of the nonbullous lung, and complements the CT scan.

Table 2. – Some of the most common causes of a carbon monoxide transfer coefficient (K_{CO}) which is lower or higher than the reference value.

Low K_{CO}	High K_{CO}
Diffuse alveolar damage	**Loss of units (discrete)**
Pulmonary fibrosis	Pneumonectomy [21, 22]
Connective tissue/ autoimmune disease	Local destruction/infiltrates
Sarcoidosis, asbestosis, bleomycin	**Incomplete alveolar expansion**
Pulmonary hypertension-associated	Pleural disease [25]
Vasculitis	Neuromuscular [20]
Thromboembolic	Chest wall deformity [26]
Congestive heart failure/ mitral stenosis	Poor technique
Pulmonary oedema	**Alveolar haemorrhage# [27]**
Intrapulmonary shunting	Anti-GBM disease
Pulmonary arteriovenous malformations	Pulmonary vasculitis
Hepatopulmonary syndrome	Wegener's granulomatosis
Airflow obstruction	SLE
Emphysema	Idiopathic haemosiderosis
Churg-Strauss syndrome	**Increased pulmonary blood flow#**
Bronchiolitis	ASD [28]
	Asthma [29]

#: $T_{L,CO}$ (% pred) may also be high; GBM: glomerular basement membrane; SLE: systemic lupus erythematosus; ASD: atrial septal defect.

The causes of a high K_{CO} are less familiar. Discrete loss of alveolar units and lack of alveolar expansion have already been discussed (table 2, fig. 2). Alveolar haemorrhage [27], redistribution of pulmonary blood flow in asthma [31] and a high cardiac output state *e.g.* atrial septal defect (ASD) [28] all increase K_{CO}. Alternatively, when the K_{CO} is high, $T_{L,CO}$ may be reduced by lack of expansion or loss of units, normal (as in asthma) or even increased (alveolar haemorrhage or ASD).

Patients with a $T_{L,CO}$ of 60% pred, for example, have a similar reduction in their gas exchange capacity at rest. Nevertheless, this defect may result from a variety of changes in K_{CO} or V_A, as shown in table 3; examining these patterns provides information on the underlying pathophysiology which will be overlooked if attention is focused solely on the $T_{L,CO}$. Further examples of these patterns are discussed in more detail elsewhere [34].

Normalizing the K_{CO} *for a low* V_A

The consequences of three different ways of normalizing the K_{CO} in disease for a current V_A of 60% of the

Table 3. – Hypothetical combinations of carbon monoxide transfer coefficient (*K*CO) and single-breath alveolar volume (*V*A,SB) giving rise to a carbon monoxide transfer factor (*T*L,CO) of 60% pred at full inflation[#]

*V*A,SB		*K*CO (*T*L/*V*A				Interpretation/suggested diagnoses
				% pred at actual *V*A[§]		
% reference TLC[#]	L BTPS	mmol·min^{-1}·kPa^{-1}·L^{-1} BTPS	% pred[#] from reference TLC	Loss of units model	Lack of expansion model	
Without airflow obstruction						
35	2.16	2.88	172	134	105	Acute neuromuscular (lack of alveolar expansion) or (if transient) alveolar haemorrhage (loss of units)
50	3.09	2.02	120	100	81	Lung resection, collapse, infiltrates (loss of units)
60	3.7	1.68	100	87	72	Diffuse alveolar damage
70	4.41	1.41	84	76	65	Diffuse alveolar damage
85	5.25	1.19	71	69	63	Pulmonary vascular pathology
With airflow obstruction						
85	5.25	1.19	71	*	*	Emphysema; Churg-Strauss vasculitis
71	4.41	1.41	84	*	*	Bronchiolitis
50	3.09	2.02	120	*	*	Bronchiectasis

[#]: *T*L,CO of 60% of predicted value (6.23 mmol·min^{-1}·kPa^{-1}) and reference values for *K*CO and predisease total lung capacity (TLC) derived from equations of ROBERTS *et al* [33] for a male aged 45 yrs and of height 1.75 m; [§]: see Figure 2b; *: inappropriate as cause of low *V*A is incomplete gas mixing; *V*A: alveolar volume; BTPS: at body pressure and ambient temperature, and saturated with water vapour.

*V*A at predisease TLC are shown in columns 4, 5 and 6 of table 3. The conventional way (column 4) is to compare the observed value with the value predicted at the predisease TLC. An alternative (column 6), proposed by STAM *et al.* [5] and FRANS *et al.* [6], is to compare the observed value with the *K*CO at the patient's actual *V*A from studies of voluntary restriction of expansion in normal subjects (fig. 1b). A third normalization procedure (column 5) compares the observed value with the expected *K*CO at a *V*A reduced by loss of lung tissue in which pulmonary blood flow per unit lung volume is high and increases the expected *K*CO (fig. 1c), but to a lesser extent than with the lack of alveolar expansion model. The same arguments apply to normalizing the *T*L,CO (fig. 2a).

The importance of choosing an appropriate model for reference values is shown in table 3. If the diagnosis is acute neuromuscular disease (first example), the appropriate model is "lack of alveolar expansion" and the observed value is 105% pred. But, if the same values of *K*CO and *V*A were due to transient alveolar haemorrhage, the appropriate reference is "loss of units" (*V*A loss due to alveolar units filled with blood) and the observed value is increased at 134% pred. In lung resection (second example), "loss of alveolar units" is again the appropriate model (100% pred), whereas the "lack of expansion model" falsely suggests a degree of alveolar damage (81% pred). The appropriate models for diffuse alveolar damage and micro vascular damage are (third, fourth and fifth examples) not obvious. Referencing the measured *K*CO to the expected *K*CO at predisease TLC results in an overestimated (or upper bound) value compared to predictions of *K*CO at the actual *V*A. Indeed, in diffuse alveolar damage, the *K*CO expressed in the conventional way may be $\geqslant$100% pred (fourth example), and familiarity with the relationships between *T*L,CO and *K*CO shown in figure 2 would be needed if a correct clinical interpretation is to be made.

Conclusions

The *K*CO is a measurement of the rate constant for alveolar uptake of CO during breath-holding in the single breath measurement of *T*L,CO at full inflation. The *T*L,CO is derived as the product of the *K*CO and the single breath alveolar volume (*V*A) divided by PB - PH_2O.

In respiratory disease, at least four different pathophysiological mechanisms are responsible for the reduction in single-breath *V*A, with only acute inspiratory muscle weakness simulating the effects of voluntary submaximal inflation of the normal lung.

With normal alveolar structure and function, the increase in *K*CO at a given low *V*A with incomplete alveolar expansion is greater than the corresponding increase due to lung resection.

The advantages and disadvantages of normalizing *K*CO (and *T*L,CO) to predisease predicted TLC (the conventional method) or to the actual *V*A using lack of expansion or loss of alveolar units models, are discussed.

As originally pointed out by KROGH [3], different combinations of alveolar volume and carbon monoxide transfer coefficient may occur in disease for a given value of carbon monoxide transfer factor, each pattern providing different pathophysiological information which would be overlooked if attention was focused solely on the carbon monoxide transfer factor.

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