In defence of the carbon monoxide transfer coefficient $K_{CO}$ ($TL/VA$)

J.M.B. Hughes, N.B. Pride


ABSTRACT: The carbon monoxide transfer factor ($TL/CO$) is the product of the two primary measurements during breath-holding, the CO transfer coefficient ($K_{CO}$) and the alveolar volume ($VA$). $K_{CO}$ is essentially the rate constant for alveolar CO uptake ($Krogh's k_{CO}$), and in healthy subjects, increases when $VA$ is reduced by submaximal inflation, or when pulmonary blood flow increases. Recently, new reference values were proposed for clinical use which included the observed $VA$ 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 $VA$ varies according to the underlying pathophysiological mechanism. The advantages and disadvantages of normalizing $K_{CO}$ and $TL/CO$ to predisease predicted TLC or to the patient's actual $VA$ (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.


A few years ago, a paper in the European Respiratory Journal [1] concluded that: "... the use of $TL/VA$ (the carbon monoxide (CO) transfer coefficient) cannot be justified on scientific grounds". Apart from one letter of disagreement [2], this view that $TL/VA$ (or $K_{CO}$) is a redundant and misleading measurement has not been challenged. This is surprising because measurements of $TL/VA$ 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 ($TL/CO$), with the uptake being measured at total lung capacity (TLC). Krogh [3] pointed out that $TL/CO$ 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 ($VA$).

$k_{CO}$ is measured as the exponential decay in fractional concentration of CO over a period of breath-holding (BHT):

$$k_{CO} = \left( \log_{e}[CO_0/CO_t] \right)/BHT$$  \hspace{1cm} (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:

$$TL/CO = [K_{CO} \times VA \ \text{STPD}] / [PB - PH_{2O}]$$  \hspace{1cm} (2)

where $PB$ and $PH_{2O}$ 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 ($PA_{CO}$). $VA$ 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.min$^{-1}$;kPa$^{-1}$;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 ($TL/VA$ or $DL/VA$). 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 ($PB - PH_{2O}$). In SI units, $k_{CO}$ (min$^{-1}$) converts to $K_{CO}$ ($TL/VA$) by dividing by 2.56.

The objection of Chinn et al. [1] to the use of $TL/VA$ is that "VA was the largest single contributor to the variance in $TL/VA$"; unfortunately, this gives the
misleading impression that $Tl/Va$ is derived from $Tl,CO$ by dividing $Tl$ by $Va$, whereas $Tl/Va$ and $Va$ are the two primary measurements used to obtain $Tl,CO$. An unambiguous way to rephrase this objection would be to say that the rate constant for CO uptake varies with $Va$, as shown (within an individual) by Krogh [3] in 1915, and confirmed by all subsequent authors.

The variation in $Kco$ with $Va$ 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 $Kco$ 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 $Tl,CO$ and $Kco$, which include a term for $Va$ (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 $Tl,CO$ when $Va$ 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 ($Kco$ and $Va$) 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 $Tl,CO$ and $Kco$. Figure 1 shows that $Kco$ and $Tl,CO$ 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 $Kco$ is linear, although earlier studies [4, 10] found a steeper rise at $Va < 50% Va,max$. Despite this increase in $Kco$, the product $Kco \times Va$ (i.e $Tl,CO$) falls as $Va$ declines. On exercise, $Kco$ (and $Tl,CO$) increases from its value at rest (cardiac output 5 L-min$^{-1}$) by ~20% per 5 L min$^{-1}$ increase in blood flow.

![Figure 1](image-url)

*Fig. 1.* – In a) the transfer factor ($Tl,CO$) and b) carbon monoxide transfer coefficient ($Kco$) are plotted against alveolar volume ($Va$) as per cent of the $Va$ 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) $Kco$ (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]). $Tl,CO$ would behave similarly.
The physiological explanation for these changes is given in the Roughton-Forster equation [11], corrected for \( VA \):

\[
\frac{VA}{T_{L,CO}} = \frac{VA}{Dm} + \frac{VA}{\theta \text{m}Q_c} \tag{3}
\]

where \( Dm \) is the membrane diffusing capacity (mmol,min\(^{-1}\)-kPa\(^{-1}\)), \( \theta \) 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\(^{-1}\)-L\(^{-1}\).

As the expansion of the lung diminishes, \( Dm \) 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 \( VA \). \( K_CO \), on the other hand, is dependent on the ratios, \( Dm/VA \) and \( Q_c/VA \). In the sitting position [12, 13], the fall in \( Dm \) is almost proportional to the fall in \( VA \), so the rise in \( K_CO \) as \( VA \) falls (fig. 1b) is dominated by the rise in \( Q_c/VA \).

Several other physiological factors influence \( K_CO \) at a given \( VA \). As cardiac output rises on exercise (fig. 1c), \( Q_c/VA \) increases by capillary distension and recruitment; \( Dm/VA \) also increases slightly because vascular distension expands the alveolar surface available for gas exchange. In contrast, anaemia, by reducing \( \theta \text{m}Q_c \) will reduce \( K_CO \) (fig. 1d) and \( T_{L,CO} \) similarly. A low alveolar oxygen tension (\( P_a,o2 \)), as occurs at altitude, will increase \( K_CO \) by increasing \( \theta \text{m}Q_c \) [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 \( \geq 90\% \) 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].

**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 \( VA \), but they cautioned that this assumes that "the effect of decreasing lung volume by disease has the same effect on \( T_{L,VA} \) as the voluntary reduction in lung volume in healthy volunteers". Some of the different mechanisms of reductions in \( VA \) 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 \( VA_{max} \) (table 1, lack of lung expansion mechanism),

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanisms</th>
<th>Prototype</th>
<th>Other examples with comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrictive disease with a small ( VA/TLC ) and normal ( VA_{max} )</td>
<td>Lack of lung expansion: lung structure normal, Loss of units: remaining lung structure normal, Diffuse alveolar damage</td>
<td>Acute inspiratory muscle weakness, Pneumonectomy, Fibrosing alveolitis</td>
<td>Chest wall disease and pleural disease, but lack of expansion is usually nonuniform, Local alveolar infiltrate or collapse, consolidation or local destruction, 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</td>
</tr>
<tr>
<td>Obstructive disease with normal or increased TLC</td>
<td>Sampled ( VA &lt; TLC ) due to incomplete mixing during breath-holding</td>
<td>Emphysema</td>
<td>Incomplete mixing may be associated with alveolar destruction, space-occupying lesions (bullae) or normal alveolar structure (asthma)</td>
</tr>
</tbody>
</table>

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 \((PL)\) at \(VA_{\text{max}}\), and preservation of a similar distribution of cardiac output and pulmonary capillary volume as in normals. Thus \(TL_{CO}\) should fall and \(KCO\) 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 \(TL_{CO}\) was 65% pred (range 44–78) and the mean \(KCO\) was 128% pred (range 101–167) at 60% of predicted maximum \(VA\); a \(TL_{CO}\) of 80–85% and a \(KCO\) of 130–140% would have been predicted on a reduced \(VA\) expansion model (fig. 1). A possible explanation for the lower \(TL_{CO}\) and \(KCO\) than expected is secondary atelectasis; the remaining aerated lung units would then be more expanded than indicated by the actual level of \(VA\), and have a lower \(KCO\).

### Loss of alveolar units

The physiological situation with a reduction in \(VA\) and TLC (table 1, loss of units mechanism) from lung resection, e.g. pneumonectomy, is completely different. First, \(PI\) 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 \(KCO\) versus cardiac output plot in fig. 1c. This relationship between \(KCO\) and pulmonary blood flow can be transposed into a plot of \(KCO\) against loss of alveolar units (as \(VA/VA_{\text{max}}\)%), where 50% \(VA_{\text{max}}\) is equivalent to the \(KCO\) for the whole lung at double the resting cardiac output (10 L·min\(^{-1}\)) and 33% \(VA\) \(_{\text{max}}\) is equivalent to a three-fold increase of blood flow per unit volume (fig. 2b). The \(TL_{CO}\) which results from these opposing changes of \(KCO\) and \(VA\) is also shown (fig. 2a).

Preservation of \(Q_{C}\) is the reason why, for a given \(VA\), \(TL_{CO}\) and \(KCO\) in figure 2 are higher in the incomplete alveolar expansion situation than for loss of alveolar units. At 50% \(VA_{\text{max}}\), for loss of units, the data of Hsu 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 \(Dm\) of 58% and a \(Q_{C}\) of 67%. On the other hand, with voluntary reduction to 50% \(VA_{\text{max}}\), \(Dm\) (as % \(Dm\) at \(VA_{\text{max}}\)) would also be 58% but \(Q_{C}\) would be 100% [12]. Both models presuppose that the alveolar units of the \(VA\) 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 \(KCO\) post-pneumonectomy:

\[
\Delta KCO \,(\%\text{pred}) = 0.41x + 2.1
\]  

(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 \(KCO\) was 110–131% for a mean \(KCO\) preoperatively of 98%. Since \(VA_{\text{max}}\) 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 \(KCO\) 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 \(KCO\) of 145–155% (fig. 2b).

### 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, $D_{VA}$
and $Q_e$ 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 $VA$ 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 $TL,CO$ on $VA$ in a
group of young males without previous pulmonary
disease, some of whom developed changes in the lungs,
accompanied by modest reductions in $TL,CO$ 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 $TL,CO$ and
$K_{CO}$ with change in $VA$ (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 $TL,CO$ 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 $VA$ ($V_A,SB$) in airflow obstruction
(table 1. $VA$ < TLC due to incomplete mixing mechan-
ism) 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 $VA$ 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 $TL,CO$, the volume ($VA$) 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 $TL,CO$)
or $V_A,SB$ (which would give a minimum or lower bound
$TL,CO$). 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 $TL,CO$ (equivalent to $K_{CO}$ x 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 $TL,CO$ ($K_{CO}$
x $V_A,SB$) excludes the poorly ventilated units (equiva-
lent to TLC - $VA$ 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 $TL,CO$ 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 ($D_{VA}/VA$) and vascular
density ($Q_e/VA$). Disease processes, which reduce
alveolar surface and capillary density (emphysema,
fibrosis), or which, more selectively, lead to loss of the

| 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 | Pneumonecctomy [21, 22] |
| Connective tissue/ autoimmune disease | Local destruction/infiltrates |
| Sarcoidosis, asbestosis, bleomycin | Incomplete alveolar expansion |
| Pulmonary hypertension-associated | Pleural disease [25] |
| Vasculitis | Neurovascular disease [26] |
| Thromboembolic | Chest wall deformity [26] |
| Congestive heart failure/ mitral stenosis | Poor technique |
| Pulmonary oedema | Alveolar haemorrhage$^a$ [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$^a$ |
| Bronchiolitis | ASD [28] |
| | Asthma [29] |

$^a$: $TL,CO$ (% pred) may also be high; GBM: glomerular basement membrane; SLE: systemic lupus erythematosus; ASD: atrial septal defect.

- microvasculature (vasculitis, intrapulmonary shunting, heart failure) reduce the $K_{CO}$ (table 2) and $TL,CO$, often severely. In practice, by using the standard reference values for $TL,CO$ at the predicted TLC, the upper or lower-bound values of $TL,CO$ 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.

- 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 hemorrhage [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, $TL,CO$ 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 $TL,CO$ 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 $VA$, 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 $TL,CO$. Further examples of these
patterns are discussed in more detail elsewhere [34].

**Normalizing the $K_{CO}$ for a low $VA$**

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

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Non-English content has been removed or translated for the purpose of this response. The original document contains comprehensive and detailed medical information, including tables and figures, which are not transcribed here for brevity and clarity.
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

<table>
<thead>
<tr>
<th>$V_{A,SB}$</th>
<th>$K_{CO}$ ($T_{L,CO}$)</th>
<th>% pred from reference model</th>
<th>% pred at actual $V_{A}$</th>
<th>Interpretation/suggested diagnoses</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Lack of expansion model</td>
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<td>Lung resection, collapse, infiltrates</td>
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<td>(loss of units)</td>
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<td>Diffuse alveolar damage</td>
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<td>Pulmonary vascular patholody</td>
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<td>Emphysema; Churg-Strauss vasculitis</td>
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<td>Bronchiolitis</td>
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<td>Bronchiectasis</td>
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</tbody>
</table>

### Without airflow obstruction

<table>
<thead>
<tr>
<th>$V_{A,SB}$</th>
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<th>Interpretation/suggested diagnoses</th>
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<tr>
<td>35</td>
<td>2.16</td>
<td>2.88</td>
<td>172</td>
<td>134 105</td>
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<tr>
<td>50</td>
<td>3.09</td>
<td>2.02</td>
<td>120</td>
<td>100 81</td>
</tr>
<tr>
<td>60</td>
<td>3.7</td>
<td>1.68</td>
<td>100</td>
<td>87 72</td>
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<tr>
<td>70</td>
<td>4.41</td>
<td>1.41</td>
<td>84</td>
<td>76 65</td>
</tr>
<tr>
<td>85</td>
<td>5.25</td>
<td>1.19</td>
<td>71</td>
<td>69 63</td>
</tr>
</tbody>
</table>

### With airflow obstruction

<table>
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<th>$V_{A,SB}$</th>
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$V_{A}$ 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 $\geq 100%$ 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 $P_b - P_{H_2O}$.

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.

**References**

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