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Transfer factor for carbon monoxide: a glance behind the scene

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Summary

The transfer factor for carbon monoxide (T_LCO) is widely used in pulmonary function laboratories because it represents a unique non-invasive window on pulmonary microcirculation. The T_LCO is the product of two primary measurements, the alveolar volume (V_A) and the CO transfer coefficient (KCO). This test is most informative when V_A and KCO are examined, together with their product T_LCO. In a normal lung, a low V_A due to incomplete expansion is associated with an elevated KCO, resulting in a mildly reduced T_LCO. Thus, in case of low V_A, a seemingly "normal KCO" must be interpreted as an abnormal gas transfer. The most common clinical conditions associated with an abnormal T_LCO are characterised by a limited number of patterns for V_A and KCO: incomplete lung expansion, discrete loss of alveolar units, diffuse loss of alveolar units, emphysema, pulmonary vascular disorders, high pulmonary blood volume, alveolar haemorrhage.

Key words: carbon monoxide transfer; pulmonary gas exchange; diffusing capacity

Introduction

The carbon monoxide transfer factor (T_LCO) is widely used in lung function laboratories where it complements the measurement of lung volumes and of forced inspiratory and expiratory flows. The T_LCO is alternatively named the diffusing capacity (D_LCO), but the former term is more appropriate for two reasons. First, this index is not uniquely determined by the diffusive characteristics of the lung, and second, it does not represent a maximal capacity in resting conditions because it easily increases with metabolic rate [1]. By measuring the surface area of the lung available for gas exchange, this test represents a unique window on the pulmonary microcirculation. Thus, the T_LCO is a key measurement in conditions like interstitial lung diseases and in the evaluation before surgery for lung cancer or for lung volume reduction in emphysema. Furthermore, in the presence of normal lung volumes and spirometry, the T_LCO may be the sole abnormal test hinting to a pulmonary vascular disorder like chronic thromboembolic disease or other causes of pulmonary vascular obliteration.

Although the usefulness of the T_LCO is not disputed, the complexity of this test is not always fully appreciated. For instance, although introduced long ago by Marie Krogh in 1915 [2], this test was still fuelling a lively scientific controversy at the dawn of the XXI century! [3–5]. The aim of this article is first to recall some neglected principles of the T_LCO, and second to propose a practical scheme of interpretation which is largely inspired by the thorough work of Hughes and Pride [4, 6].

Glossary:

CO:	carbon monoxide
T_LCO:	carbon monoxide transfer factor (synonym: D_LCO = carbon monoxide diffusing capacity)
T_LCO_{SB}:	T_LCO measured by the single-breath method
kCO:	rate constant for alveolar-capillary CO transfer (= permeability factor)
KCO:	carbon monoxide transfer coefficient
V_A:	alveolar volume
TLC:	total lung capacity
D_M:	membrane conductance
θ:	rate of reaction of CO with haemoglobin
Qc:	pulmonary capillary blood volume
P_B:	barometric pressure
P_{H2O}:	water vapour pressure
STPD:	standard temperature (0 °C) and pressure (760 mm Hg), dry
BTPS:	body temperature (37°C) and pressure (P_B) saturated with water vapour

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Measurement

The T_LCO measures the rate of transfer of CO from the alveoli to the blood. Inhaled carbon monoxide is used because of its very high affinity for haemoglobin: as a result, the plasma CO partial pressure remains close to zero, the gradient of partial pressure remains operational between the alveoli and the capillary blood, and the amount of CO transferred is limited by diffusion only. The single-breath T_LCO measurement (T_LCO_{SB}) was introduced by Ogilvie et al. [7] and will be described here because it is the most widely used method.

The subject first fully exhales, then takes a rapid and full inspiratory vital capacity of a gas mixture composed of air, a tiny fraction of CO (0.003) and a fraction of an inert gas such as helium or methane. The breath is held for 10 seconds at complete inspiration before a rapid and full exhalation is made. After the first portion of exhaled gas has been discarded, gas is collected during mid-expiration as an alveolar sample for analysis of CO and of the inert gas. It is very important to control the quality of the manoeuvre by checking several points: that the inspiration is rapid enough (<2.5 s, or <4 s in case of airflow limitation), that the inspired volume is large enough (>90% vital capacity), and that the breath-holding time is correct (10 ± 1 s). From this, two primary measurements are made:

Rate constant for alveolar-capillary CO transfer (= permeability factor, kCO):

The initial alveolar fraction of CO is calculated as follows:

$$F_ACO_0 = F_ICO \cdot (F_AHe / F_IHe)$$

where: F_ICO = inspired fraction of CO
F_AHe = alveolar fraction of helium
F_IHe = inspired fraction of helium

During breath-holding, the alveolar fraction of CO decreases exponentially:

$$F_ACO_t = F_ACO_0 \cdot e^{-kt}$$

The permeability factor is calculated as follows:

$$kCO = \frac{\log_e (F_ACO_0 / F_ACO_t)}{t}$$

where the unit for kCO is: min^{-1}

Alveolar volume (V_A):

$$V_A = V_I \cdot \frac{F_IHe}{F_AHe}$$

where: V_I = inspired volume
the unit for V_A is: ml STPD

The T_LCO is then calculated as the product of the permeability factor and alveolar volume, divided by the effective barometric pressure:

$$T_LCO = \frac{kCO \cdot V_A}{P_B - P_{H2O}}$$

where: P_B = barometric pressure
P_{H2O} = water vapour pressure

The T_LCO is expressed in units of conductance:

mmol CO · min^{-1} · kPa^{-1} (or ml CO · min^{-1} · mm Hg^{-1} in traditional units).

It is important to understand that the T_LCO is not the measurement of an actual physical variable. Rather, it is a calculation of what would be the flux of CO from the alveoli to the blood in the hypothetical condition of the subject's lungs being filled with 100% CO (which, if true, would expose to medico-legal consequences). Hence the introduction of alveolar volume which represents the volume of distribution of CO, and of barometric pressure which corresponds to the driving pressure for diffusion [6].

Theoretical considerations

Components of T_LCO

The T_LCO is made of two conductances in series: the *membrane conductance (D_M)* which represents the diffusion component, and the *reactive conductance ($\theta \cdot Qc$)* where θ is the rate of reaction of CO with haemoglobin and Qc is the blood volume in the pulmonary capillaries. The D_M factor is reduced when the alveolar-capillary membrane surface is reduced or when its thickness is increased. The θ factor varies with the concentration of haemoglobin: the low value of θ explains the low values of T_LCO measured in anaemia [8].

Confounding factors

Because of the effect of haemoglobin concentration [Hb], T_LCO has to be adjusted to the normal [Hb] in particular when anaemia is present or can be suspected. The adjusted value (T_LCO adj. or T_LCO corr.) is considered for assessing gas exchange.

Carboxyhaemoglobin (HbCO) reduces T_LCO by two mechanisms: first, it decreases the CO pressure gradient by increasing venous CO back pressure, and second, it decreases the mass of haemoglobin available for CO binding. The effect is a 1% fall of T_LCO for each 1% increment of [HbCO]. To avoid this problem it is recommended that the

subject refrains from smoking 24 hours before the test.

The T_LCO is influenced by altitude because oxygen and CO are in competition for Hb: θ increases when alveolar PO_2 falls. Thus, T_LCO increases by 0.31% per mm Hg decrease in inspired PO_2. This point has to be considered when the test is performed in a pulmonary function laboratory located at high altitude.

Exercise increases T_LCO by increasing pulmonary capillary blood volume (Qc). Thus, T_LCO increases by 20% for each increment of 5 L · min^{-1} of cardiac output. It is recommended that the subject refrains from strenuous exercise and remains seated for at least 5 min before testing [9].

The problem of V_A in airflow limitation

Patients with chronic obstructive pulmonary disease (COPD), in particular those with emphysema, tend to have a higher than normal total lung capacity (TLC). Yet, the alveolar volume (V_A) measured during the T_LCO_{SB} manoeuvre is low. This discrepancy between V_A and TLC is due to uneven ventilation distribution during the short breath-holding time leading to an incomplete mixing between the inspired gas and the residual volume gas. Indeed, the more severe is airflow limitation, the higher is the underestimation of TLC by V_A. As T_LCO is the product of kCO and V_A divided by effective barometric pressure, this results in an underestimation of the potential true T_LCO of the patient. However, the degree of underestimation is unknown, because poorly ventilated units are likely to be more severely affected by the disease. This is an inherent limitation of the T_LCO_{SB} in COPD. To circumvent this problem it has been proposed to use the V_A measured by plethysmography [1]. However, this would lead to an overestimation of true T_LCO because it would include poorly ventilated units and assign them a kCO equal to that of well ventilated units [4]. Moreover, this dual method is impractical and is consequently not applied.

What is KCO (or T_LCO/V_A)?

The carbon monoxide transfer coefficient (KCO) is often written as T_LCO divided by alveolar volume (T_LCO/V_A). It is important to grasp what KCO actually represents. If we take the equation for T_LCO:

$$T_LCO = \frac{kCO \cdot V_A}{P_B - P_{H_2O}}$$

then, dividing by V_A:

$$KCO = T_LCO/V_A = \frac{kCO \cdot V_A}{(P_B - P_{H_2O}) \cdot V_A} = \frac{kCO}{P_B - P_{H_2O}}$$

the units for KCO are: mmol CO · min^{-1} · kPa^{-1} · L^{-1}, or ml CO · min^{-1} · mm Hg^{-1} · L^{-1} in traditional units. In the latter case, note that V_A is expressed in ml STPD in the numerator because it represents a volume of CO, and in L BTPS in the denominator because it represents a volume of air.

Thus, the *transfer coefficient KCO* is simply another way to express the *permeability factor kCO*, one of the two primary measurements allowing to derive T_LCO [4, 6].

The expression T_LCO/V_A is misleading because it implies a "correction of T_LCO for alveolar volume". According to this view, a low T_LCO with a low V_A and a normal KCO (or T_LCO/V_A) would be interpreted as a lung of reduced volume but with normal transfer of CO. This is definitely wrong because in a normal lung, KCO increases exponentially when alveolar volume is reduced, as during a voluntary incomplete expansion, or during a reduced expansion in a patient with a neuromuscular disorder (Figure 1). This is due to an increase in the surface to volume ratio for diffusion per alveolus as the alveoli become smaller. Thus, when V_A is low, a seemingly "normal KCO" actually reflects an abnormal gas transfer.

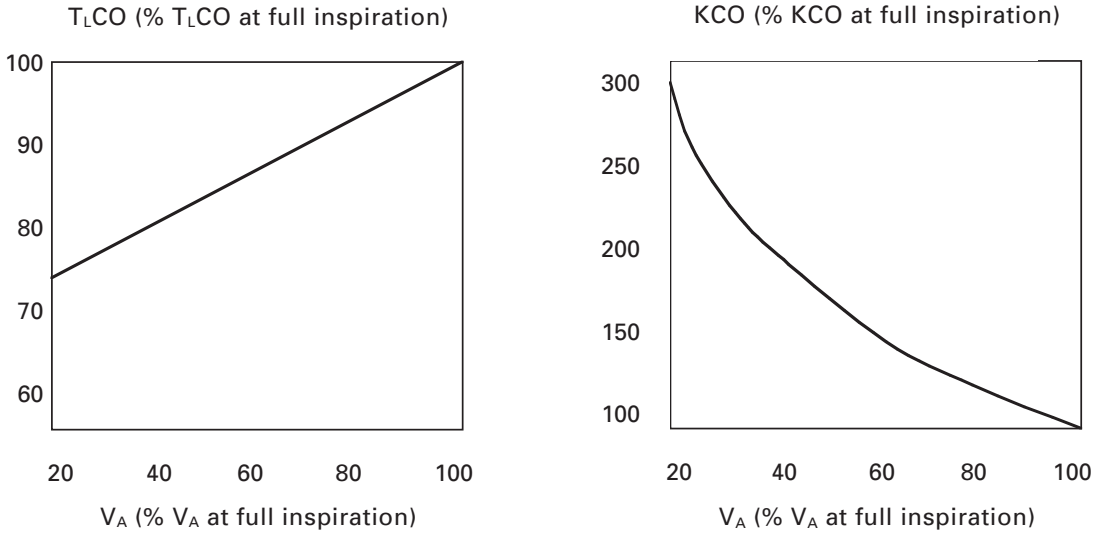

Figure 1

Variation of carbon monoxide transfer coefficient (KCO) and transfer factor (TLCO) with lung expansion in normal subjects. The KCO, T_LCO and alveolar volume (V_A) are expressed in percent of values measured at full inspiration. The KCO increases exponentially with decreasing V_A. As a result, T_LCO decreases only mildly with decreasing V_A.

Practical considerations for interpretation of T_LCO

From the preceding considerations, it appears that the interpretation of T_LCO is unfortunately not straightforward. Nevertheless, this test is highly informative and useful if the following steps are taken [6]:

First, the quality of the manoeuvres must be scrupulously checked. This is now made easy by the display of error codes. A common failure is an insufficient inspired volume, whereas it should exceed 90% of vital capacity.

Second, KCO and V_A should be considered as the primary measurements and should be analysed along with T_LCO. The relationship between these variables can be seen as follows:

KCO	·	V_A	=	T_LCO
efficiency per lung unit		*number of contributing units*		*gas exchange capacity*

For practical purposes, the most common disorders affecting T_LCO can be grouped in a limited number of pathophysiological or clinical entities.

1) Incomplete lung expansion

The lung is normal but incompletely inflated, like in neuromuscular disorders, obesity, kyphoscoliosis, pleural effusion, or in case of a poorly performed test. The low V_A is associated with an elevated KCO. As a result, T_LCO is only mildly reduced, falling by 3% per 10% fall in V_A.

Case 1: 57-year-old man, acid maltase deficiency:

Vital capacity	50% pr.	V_A	64% pr.
Total lung capacity	65% pr.	KCO	141% pr.
FEV_1	52% pr.	T_LCO	91% pr.
FEV_1/FVC	100% pr.		

Case 2: 52-year-old woman, obesity (BMI = 64 kg · m^{-2}):

Vital capacity	84% pr.	V_A	63% pr.
Total lung capacity	72% pr.	KCO	143% pr.
FEV_1	61% pr.	T_LCO	91% pr.
FEV_1/FVC	106% pr.		

2) Discrete loss of alveolar units

There is a discrete loss of lung, for instance a whole lung, a lobe, or several units in several lobes, but the lung remaining is normal. Examples are pneumonectomy, lobectomy, lobar collapse, local destruction (post-TB, bronchiectasis), localized alveolar infiltrate (sarcoidosis). The loss of alveolar units is reflected by a low V_A. Because blood flow of lost units is diverted to remaining units, KCO increases slightly. As a result, T_LCO falls relatively less than V_A.

Case 3: 62-year-old man, post-pneumonectomy (right lung):

Vital capacity	43% pr.	V_A	45% pr.
Total lung capacity	55% pr.	KCO	110% pr.
FEV_1	45% pr.	T_LCO	50% pr.
FEV_1/FVC	104% pr.		

3) Diffuse loss of alveolar units

The alveolar units most severely affected by the disease are lost, but the remaining lung is affected as well by the disease. Examples are diffuse fibrosis (idiopathic pulmonary fibrosis, connective tissue diseases, pneumoconiosis), alveolar infiltrates (inflammatory infiltrate, hypersensitivity pneumonitis, pneumocystis carinii pneumonia), cardiovascular disorders (pulmonary oedema, chronic heart failure). The V_A is low, KCO is low to "normal", and T_LCO is markedly reduced.

Case 4: 79-year-old man, pulmonary asbestosis:

Vital capacity	59% pr.	V_A	47% pr.
Total lung capacity	60% pr.	KCO	79% pr.
FEV_1	65% pr.	T_LCO	37% pr.
FEV_1/FVC	109% pr.		

Case 5: 75-year-old man, idiopathic pulmonary fibrosis:

Vital capacity	73% pr.	V_A	60% pr.
Total lung capacity	66% pr.	KCO	98% pr.
FEV_1	77% pr.	T_LCO	59% pr.
FEV_1/FVC	105% pr.		

Case 6: 73-year-old man, chronic heart failure:

Vital capacity	86% pr.	V_A	76% pr.
Total lung capacity	96% pr.	KCO	80% pr.
FEV_1	81% pr.	T_LCO	61% pr.
FEV_1/FVC	95% pr.		

Case 7: 45-year-old man, systemic lupus erythematosus with interstitial lung infiltrate and diaphragm weakness:

Vital capacity	46% pr.	V_A	45% pr.
Total lung capacity	63% pr.	KCO	104% pr.
FEV_1	50% pr.	T_LCO	47% pr.
FEV_1/FVC	109% pr.		

Comment: the interstitial lung disease and the diaphragm weakness both contribute to a low V_A. In case of diaphragm weakness with a normal lung, the KCO would be elevated, whereas the seemingly "normal" value observed here reflects the effect of interstitial disease.

4) Obstructive lung disease

The V_A is low because of incomplete mixing between the inspired gas and the residual volume gas during the short breath-holding time. The KCO differs according to the underlying disease. In emphysema, KCO is low because of the loss of alveolar-capillary surface. As a result, T_LCO is se-

verely reduced. In contrast, KCO may be increased in asthma where the pulmonary microcirculation is preserved and cardiac output may be increased.

Case 8: 76-year-old man, pulmonary emphysema:

Vital capacity	68% pr.	V_A	65% pr.
Total lung capacity	118% pr.	KCO	26% pr.
FEV_1	30% pr.	T_LCO	17% pr.
FEV_1/FVC	44% pr.		

5) Pulmonary vascular disorders

Examples are pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, vasculitis, sickle-cell disease, hepatopulmonary syndrome. The V_A is normal or near normal, KCO is reduced due to the vascular disorder, and T_LCO is reduced approximately to the same degree.

Case 9: 52-year-old woman, chronic thromboembolic pulmonary hypertension:

Vital capacity	123% pr.	V_A	98% pr.
Total lung capacity	105% pr.	KCO	56% pr.
FEV_1	101% pr.	T_LCO	55% pr.
FEV_1/FVC	88% pr.		

Case 10: 24-year-old woman, Takayasu's disease:

Vital capacity	88% pr.	V_A	84% pr.
Total lung capacity	95% pr.	KCO	74% pr.
FEV_1	79% pr.	T_LCO	62% pr.
FEV_1/FVC	95% pr.		

6) Increased pulmonary blood volume

Both KCO and T_LCO are mildly to moderately increased when pulmonary capillary blood volume is increased, as in case of high cardiac output or of left-to-right shunt.

7) Alveolar haemorrhage

Intermittent alveolar haemorrhage occurs in anti-GBM disease, pulmonary vasculitis, systemic lupus erythematosus, and idiopathic haemosiderosis. The V_A is mildly reduced by alveolar filling with blood, and KCO is markedly increased because inhaled CO reacts with extravascular haemoglobin. The KCO often increases to more than 150% of predicted, and a 30% increase in KCO over baseline values is suggestive of alveolar haemorrhage [10]. After haemorrhage ceases, the halftime of the return of KCO to baseline is 24 hours. It is essential to adjust KCO and T_LCO to a normal haemoglobin concentration because of fluctuating anaemia in these patients [6].

Thus, by analysing V_A, KCO and T_LCO together one is able to discriminate between the most common abnormal patterns (Table 1). Although not straightforward, this analysis of T_LCO is worth the effort because major therapeutic decisions may depend on this test, like performing surgery or initiating immunosuppressive or cytostatic therapy.

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Table 1
Common abnormal patterns of carbon monoxide transfer factor.

Condition	VA	KCO	TLCO
Incomplete lung expansion	↓↓↓	↑↑	↓
Discrete loss of alveolar units	↓↓↓	↑	↓↓
Diffuse loss of alveolar units	↓↓	↓	↓↓↓
Pulmonary emphysema	↓	↓↓	↓↓↓
Pulmonary vascular disorders	normal	↓↓	↓↓
High pulmonary blood volume	normal	↑	↑
Alveolar haemorrhage	↓	↑↑↑	↑↑

Single-breath method. VA: alveolar volume; KCO: carbon monoxide transfer coefficient; TLCO: carbon monoxide transfer factor.

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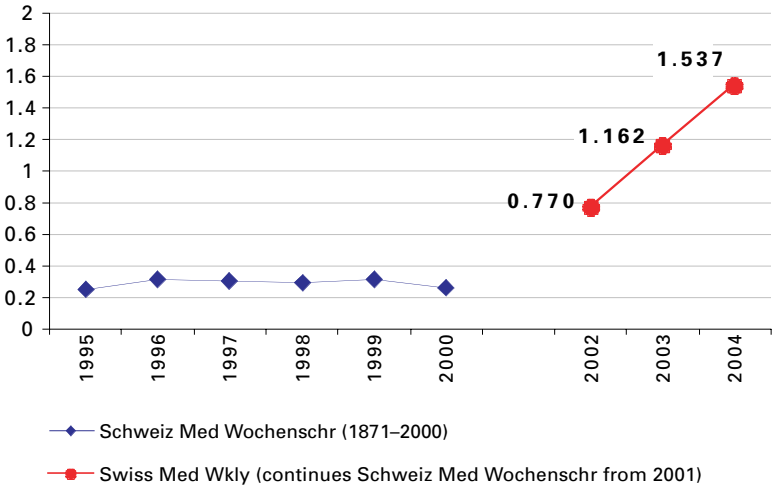

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