

# Chapter 8 - Transfer Factor for Carbon Monoxide

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## Professional Skills

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Upon completion of this chapter, the reader will be expected to:

- Understand the structure-function relationships determining gas exchange and CO Transfer Factor
  - Understand the methods available for estimating CO Transfer Factor by single-breath, exhalation and rebreathing methods
  - Understand the concepts of subdivisions of CO Transfer Factor
  - Understand the need for calibration and quality assurance
  - Understand the physiological variability in the method in normal subjects
  - Understand the differences between the methods described
  - Be able to perform the single-breath breath-hold measurement
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### 8.1 Introduction

The primary role of the lungs is the exchange of gas between the atmosphere and the pulmonary circulation, and hence meeting the  $O_2$  demands of the respiring tissues. In the reverse direction,  $CO_2$  produced by the respiring tissues is exchanged between the pulmonary circulation and the atmosphere (Chapter 2).

The gas exchange characteristics of the lungs, including the factors that contribute to the reaction rate of gases with haemoglobin, are assessed by the measurement of transfer factor of the lung (TL), which measures:

- Ventilation of the airways and some air spaces by bulk flow of gas
- Mixing and diffusion in the alveolar ducts, air sacs and alveoli

- Transfer of gases across the gaseous to liquid interface of the alveolar membrane
- Mixing and diffusion in the lung parenchyma and alveolar capillary plasma
- Chemical reaction with constituents of blood
- Circulation of blood between the pulmonary and systemic vascular beds

The capacity of the lungs to exchange gas is the result of the structural and functional dimensions of each of the processes involved in gas exchange. Structural dimensions include lung volume, path length, membrane thickness, surface area and the volume of blood in the pulmonary capillaries. Function dimensions include the level of ventilation and perfusion and the matching of ventilation to perfusion, the haemoglobin concentration, the time the red blood cell spends within the pulmonary capillary (transit time), the characteristics of the alveolar-capillary membrane and the chemical reaction rates of the gas with haemoglobin.

Measurement of TL therefore provides information about the amount of functioning capillary bed in contact with ventilated alveoli and reflects the presence of certain types of pulmonary vascular and parenchymal disorders. Ideally, we would wish to measure TL for O<sub>2</sub>, as this is the gas we breathe in. However, although TL<sub>O<sub>2</sub></sub> can be measured, it is more difficult and is therefore not used in clinical practice. As a surrogate marker of O<sub>2</sub> gas exchange function, carbon monoxide (CO) is used.

## 8.2 Historical Development CO Transfer Factor (TL<sub>CO</sub>)

There are four methods of estimating TL<sub>CO</sub> that have been developed – breath-holding, rebreathing, exhalation method and steady-state. Whilst the steady-state method is the most physiologically based, it is no longer used and therefore no further discussion on this method will be given.

The use of CO was first introduced by Christian Bohr in 1909. Based on his realization that the affinity of Hb for CO was considerably greater than the affinity of Hb for O<sub>2</sub>, and that if low concentrations of CO in alveolar gas were used, the back-pressure exerted by the carboxyhaemoglobin (COHb) in the pulmonary capillary blood could be ignored. This removed the need for arterial blood gas sampling to estimate the partial pressure of arterial CO (P<sub>CO</sub>) and simplified the calculations.

The first major development of TL<sub>CO</sub> measurements was published in 1915 [1, 2]. August and Marie Krogh had a long-running battle with Bohr over whether O<sub>2</sub> was secreted from the alveoli to the blood or passed by diffusion. Based on the assumption that - “*an essentially indifferent gas, like carbon monoxide, must pass through the alveolar epithelium by diffusion alone*” they devised a two collection method which included a period of breath holding. Having solved the disagreement, the measurement disappeared until the 1950’s when Roughton and Forster developed the measurement further.

Forster *et al* [3] added helium to the Krogh method and modified it to a single gas collection at the end of a known period of breath holding [4]. These important additions allowed the estimate of the alveolar P<sub>CO</sub> at the start of the test using the dilution of He to account for the dilution of CO by the residual volume.

The most significant and influential paper was by Ogilvie *et al* [5]. They incorporated the earlier modifications of Forster *et al* [3], enumerated some of the many factors that affect TL<sub>CO</sub> and described the “standardized” technique for the single-breath breath holding measurement of TL<sub>CO</sub>. Modifications to this “standardized” measurement include changes to the way alveolar volume (V<sub>A</sub>) is calculated and the calculation of K<sub>CO</sub> [6] and the way in which the breath-hold

time is calculated [7]. Further investigations in the 1960's included the effects of exercise, temperature, stress, and circadian rhythms.

Running alongside developments in the single breath method were similar developments in rebreathing methods. Kruhoffer [8] developed the first rebreathing method using a 6 litre bag and requiring the subject to breathe at a rate of 25 breaths.min<sup>-1</sup>. Alveolar volume was estimated using hydrogen. Lewis *et al* [9] modified this technique, used continuous analysis of the gases within the test gas bag and required 30 breaths.min<sup>-1</sup> over 30 – 45s rebreathe. Further modifications took place, notably by Marshall [10] and by Clarke *et al* [11]. The Clarke method will be described latter.

A more recent development is that of exhalation transfer factor [12]. With the advent of rapid CO analyzers, the exhaled CO could be continuously monitored throughout a controlled exhalation. This technique was developed on the basis that there are fundamental flaws in the way in which the single-breath breath holding measurement is performed and that the calculations for TL<sub>CO</sub> are problematic. By performing exactly the same manoeuvre as the single-breath method, but instead of breath-holding, the subject exhales at a constant rate from TLC to RV, then exhaled CO and the inert gas can be monitored. An outline of the method will be described latter.

One final important development in the understanding of TL<sub>CO</sub> is that it can be divided into a number of subcomponents - the diffusing membrane capacity (D<sub>M</sub>), the pulmonary capillary blood volume (V<sub>C</sub>) and the reaction rate of CO with haemoglobin (Θ), and that these may be estimated [13]. An outline of the method will be described later.

### 8.3 Terminology and Units

The terminology used is 'transfer factor' or 'diffusing capacity'. The former is used principally in Europe, whilst the latter is used in North America. Neither term is adequate to fully describe the processes involved.

The term '*transfer factor*' describes the rate of transfer of gas between the alveoli and the erythrocytes in the alveolar capillaries, the units being the quantity of gas per unit time per unit difference (gradient) between the two sites. The term '*diffusing capacity*' implies that the uptake of the test gas is at maximum capacity, i.e. the resultant figure is the highest possible. This is not the case at rest.

The SI unit of transfer factor is the mmol.min<sup>-1</sup>.kPa<sup>-1</sup>, and represents the uptake of a gas (mmol.min<sup>-1</sup>) per unit pressure gradient (kPa). The SI unit of transfer coefficient (K<sub>CO</sub>) is the mmol.min<sup>-1</sup>.kPa<sup>-1</sup>.l<sup>-1</sup> and is supposed to represent the uptake of CO per litre of alveolar volume. For conversion of SI units to traditional units, divide by 0.335.

### 8.4 Choice of Gases

The measurement of TL requires a gas mixture containing the actual test gas – CO and an insoluble gas that provides estimates of alveolar volume. In addition, further gases may be added to estimate pulmonary blood flow, this currently being acetylene (C<sub>2</sub>H<sub>2</sub>).

Carbon Monoxide has several important characteristics that make it useful:

1. The membrane diffusion coefficient and the rate of reaction of CO with haemoglobin are similar to and linearly related to that of O<sub>2</sub>.
2. Oxygen and CO bind to the same site on the haemoglobin molecule and therefore the same information can be obtained with CO as with O<sub>2</sub>.
3. The endogenous levels of CO present in the blood are low in normal non-smoking subjects. If we ignore the capillary P<sub>CO</sub>, this makes the calculation of CO uptake simpler.
4. The carboxyhaemoglobin dissociation curve is such that even after large amounts of CO have combined with haemoglobin the partial pressure of CO is very low.
5. The oxyhaemoglobin and carboxyhaemoglobin dissociation curves are affected by the temperature of the lung and the prevailing levels of O<sub>2</sub>, CO<sub>2</sub>, pH and 2-3 DPG in the same way.
6. The affinity of haemoglobin for CO is about 210 times greater than for O<sub>2</sub>. Thus, the partial pressure of O<sub>2</sub> remaining in the physiological state is not an interfering factor.
7. Low concentrations of CO are easily analyzed using infra-red gas analysis.
8. The use of CO in trace quantities does not result in any harm to the subject.

The inert, insoluble gas is used to provide estimates of the alveolar volume, which form part of the calculation of TL<sub>CO</sub>. Commonly this is helium, although argon, neon and methane are used. All these gases are chemically stable, almost inactive and although a small leakage can occur into the blood, this amount is negligible within the test time.

The composition of the gas mixture chosen will be partly dependant on the supplier of the transfer factor equipment and the working ranges of the analyzers provided. However, in general the mixture will contain 0.28 – 0.30% CO, 9 – 14% Helium, 18% O<sub>2</sub> and the remainder being nitrogen. If methane is used in place of helium, then this will be approximately 0.30%.

Inhaled O<sub>2</sub> has been standardized to approximately 18%. When ordering a gas mixture for a CO/He combination, it is not necessary to have the O<sub>2</sub> specifically analyzed, as it will approximate 18%. If we assume the atmosphere contains 20.94% O<sub>2</sub> then –

$$\%O_2 = [100 - (14.0 + 0.28)] \times 20.94 = 17.9\%$$

$$\%O_2 = [100 - (10.0 + 0.28)] \times 20.94 = 18.8\%$$

The gas **must** be produced under a medical quality products license. This license ensures the level of purity of the gas is suitable for use in humans.

## 8.5 Derivation of Indices

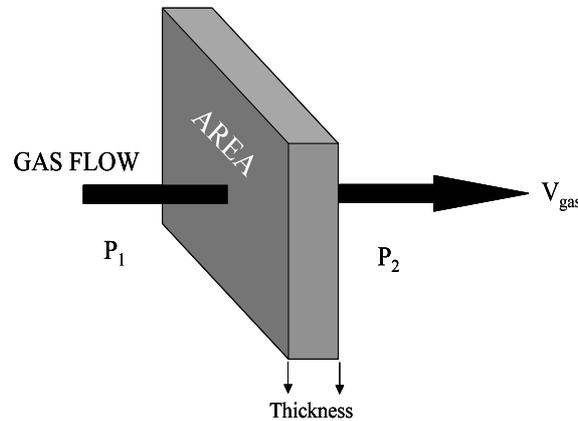
Diffusion of a substance in fluids (liquids or gases) is a passive process occurring between regions of differing gas concentrations. If a membrane of constant thickness and permeable to a particular gas is placed between two fluid compartments the diffusion of a gas across the membrane is described by Fick's law of diffusion, which states:

*"The transfer of a solute by diffusion is directly proportional to the cross-sectional area available for diffusion and to the difference in concentration per unit distance perpendicular to that cross-section"*

Thus,

$$\dot{V}_{\text{Gas}} = \frac{kA}{t} (P_1 - P_2) \quad (8.1)$$

This law is illustrated in Figure 8.1. The amount of gas transferred is proportional to the area (A), diffusion constant (k) and the partial pressure difference ( $P_1 - P_2$ ) and is inversely proportional to the thickness (t). The constant (k) is proportional to the gas solubility and inversely proportional to the square root of the molecular weight of the gas.



**Figure 8.1.** The relationship of the uptake of gas across a membrane of known surface area and thickness, to the pressure difference across the membrane ( $P_1 - P_2$ )

The driving force for the rate of gas diffusion ( $\dot{V}$ ) is the difference in the partial pressure of the gas between the two compartments ( $P_1 - P_2$ ). Thus, for a given driving force, the membrane characteristics (k, A and t) determine the rate of gas transfer. However, these characteristics are not directly applicable to the lungs due to their complex morphology and dynamic state. They are therefore combined into a single term - the transfer factor of the lungs ( $T_L$ ), so equation 8.1 becomes -

$$\dot{V} = T_L (P_1 - P_2) \quad (8.2)$$

Rearranging for  $T_L$  -

$$T_L = \frac{\dot{V}}{(P_1 - P_2)} \quad (8.3)$$

Thus,  $T_L$  may be obtained by knowing the rate of gas uptake and the partial pressures of the gas in the alveoli ( $P_1$ ) and in the capillaries ( $P_2$ ). Since the level of CO in blood is generally negligible,  $P_2$  may be regarded as being zero. However, in smokers and others exposed to high levels of environmental CO, a correction may need to be applied, but this is not needed for routine clinical practice. Equation 8.3 therefore reduces further to -

$$T_L = \frac{\dot{V}}{P_1} \quad (8.4)$$

resulting in  $T_L$  being easily estimated if the uptake of the gas is measured and its partial pressure in the alveoli is known. We cannot directly measure either of these. However,  $T_L$  is positively correlated with lung volume, so  $T_L$  may be represented as the product of the alveolar volume ( $V_A$ ) and the transfer coefficient of the lung (K), where K represents the rate of change in alveolar CO concentration (with respect to time) per litre alveolar volume, divided by the partial pressure of alveolar CO. Thus, equation 8.4 becomes -