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Can the measurement of pulmonary diffusing capacity for nitric oxide replace the measurement of pulmonary diffusing capacity for carbon monoxide?

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ABSTRACT

Pulmonary diffusing capacity for carbon monoxide (DLCO) has been an important pulmonary function test used since the 1950's. It measures the uptake of CO from the alveolar space into pulmonary capillary blood, following the same path as oxygen. It's used to evaluate/follow the progress of various lung diseases. In the eighties, a new test was developed similar to the DLCO test: pulmonary diffusing capacity for nitric oxide (DLNO). About 81–90% of the variance in DLNO is shared by DLCO in patients with cardiopulmonary disease and in healthy subjects. When DLNO is abnormally low, so is DLCO, and when DLNO is normal, so is DLCO (Kappa Statistic = 0.69, n = 251). The probability that DLNO and DLCO will be abnormally low when a cardiopulmonary disease is present (sensitivity) is 79% and 68%, respectively. The DLNO test avoids many technical issues associated with the measurement of DLCO: (1) DLNO is relatively unaffected by inspired oxygen concentration or ambient pressure, (2) DLNO is unaffected by carboxyhemoglobin, (3) DLNO is minimally affected by hemoglobin (Hb) concentration, thus correcting for Hb is not needed. (4) DLNO is more affected by lung volume compared to DLCO, thus DLNO divided by alveolar volume (KNO) is a better measure than KCO in those with restrictive lung disease, and (5) DLNO is a more stable measure over time compared to DLCO. Therefore, DLNO has several advantages over DLCO in the management of patients and could replace the DLCO test in most cases moving forward.

1. Introduction

The determination of pulmonary diffusing capacity for carbon monoxide (DLCO) is a crucial element in the daily practice of pulmonary physicians. It is used as a screening tool for multiple pulmonary pathophysiological disorders. More than that, the DLCO is a tool in the follow up of patients with interstitial lung disease, pulmonary hypertension, obstructive lung disease, and some orphan lung disease. In subjects with "*dyspnea e causa ignoti*", the combined spirometry and DLCO helps the clinician in guiding towards the right diagnostic track (Hughes and Pride, 2012).

Although the DLCO measurement is recommended in daily practice, the underlying physiological principles are not fully understood by many physicians who use this measurement. The DLCO is the uptake of CO that can pass through the lung per mmHg of partial pressure per minute. In physical terms, it is a conductance; the higher the conductance, the larger the uptake of CO. Focusing on the alveolar-capillary membrane, the flow depends on the transport as a free gas in the alveoli, the alveolar-capillary membrane, the plasma, and on its reaction with haemoglobin after its diffusion in the red blood cell. This reaction is the motor diffusion process. The carboxyhemoglobin formation is highly dependent on the presence of oxygen. Thus the interpretation of DLCO demands more reasoning than simple raw data like height and weight.

This schematic description of CO transport led Roughton and Forster to split the conductance of CO into two separate conductance's in series (Roughton and Forster, 1957). The first conductance is due to the transport of free CO through the alveolar-capillary membrane, otherwise known as alveolar-capillary membrane diffusing capacity for CO (DmCO) and the blood conductance (DbCO) characterized by the rate of reaction of CO with haemoglobin (Hb) in lung capillaries, usually θCO (the specific conductance in the blood for CO). The concentration of Hb in the pulmonary capillaries is proportionate to pulmonary capillary lung volume (Vc). The Vc is the clinically pertinent parameter. Thus DbCO is θCO·Vc provided that the concentration in Hb is normal. In its early definition, the only obstacle to CO transport as a free gas

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was considered to be the alveolar-capillary membrane, explaining the use of "m" in DmCO. In fact the flow of CO can be hampered by a long path in distended alveoli like in emphysema and by an increase in the amount of plasma between the inner part of the capillary and the inner part of the red cell.

The driving force in this diffusion process is the pressure gradient over the alveolar-capillary membrane, which is determined (on the capillary side of the membrane) by the reaction of the gas with Hb. A slow rate of reaction with Hb would favour a relative limitation of diffusion with the blood, and a high rate reaction with Hb would favour a relative limitation of the alveolar-capillary membrane. For example, oxygen has a relatively high rate of reaction with Hb in hypoxia and a low rate in hyperoxia, therefore oxygen transfer is more limited by the alveolar-capillary membrane in hypoxia than hyperoxia. If one compares nitric oxide (NO) and CO, NO would be more sensitive to an abnormality of the alveolar-capillary membrane than CO.[1] Conversely, CO would be more sensitive to an abnormality of the pulmonary capillaries than NO. A quantitative analysis of the sensitivities of these transfers shows that the transfer of NO is nearly equally sensitive to membrane and blood conductance as CO is clearly mainly sensitive to the blood conductance (Martinot et al., 2015). It has been typical but incorrect to consider DLCO as a sensitive marker of a defect of the alveolar-capillary membrane.

In 1983-84, the first abstracts were published describing a novel measure of assessing the transfer of a gas from the alveoli to the blood, called the gas transfer factor of the lung for nitric oxide, or TLNO (Borland et al., 1983, 1984).[2] In 1987, the first peer reviewed paper on TLNO was published originating from France (Guénard et al., 1987) and the British group finally published their work soon after (Borland and Higenbottam, 1989).

In the first peer-reviewed paper on DLNO, Guénard and colleagues determined that when inspiring a small amount of NO (~8 ppm) along with the traditional diffusion mixture (0.3% CO, 10% He, 21% O_2, balance N_2) simultaneously, one could estimate pulmonary capillary blood volume (Vc) and alveolar-capillary membrane diffusing capacity for CO (DmCO) (Guénard et al., 1987). This offered an advantage over the traditional two-step Roughton and Forster technique (Roughton and Forster, 1957), as the one-step NO-CO method could obtain Vc and DmCO in a single manoeuvre, reducing the carboxyhemoglobin build-up, and having similar gas distribution throughout the lung over the same cardiac output. By knowing a few assumptions, like the diffusivity ratio of NO to CO, and knowing the specific conductance of the blood for NO (θNO) and CO (θCO), and estimating the haemoglobin concentration of the patient and the alveolar oxygen pressure during a breath-hold manoeuvre (~100 mmHg), Vc and DmCO could be calculated (See Fig. 1A and B).

As the DLNO/DLCO ratio is weighted towards the DmCO/Vc ratio (Hughes and van der Lee, 2013), it has been argued that the calculation of DmCO and Vc may not be necessary and that the DLNO/DLCO ratio is a good substitute for the DmCO/Vc ratio (Hughes and van der Lee, 2013) However, it has also been argued that the DmCO and Vc components:

> "*. . .have always been more of a physiological understanding of the pathophysiological basis of disease than a clinical interest in altering treatment. . ..clinicians have done quite well by following the DLCO as a global index for patient management in both pulmonary vascular and parenchymal diseases. Partitioning DmCO and Vc is not likely to alter treatment.*" (Dr. Connie Hsia, University of Texas Southwestern Medical Center, December 2004, personal communication).

Thus, if the DLNO/DLCO ratio (DmCO/Vc ratio) has not been proven to be an important component in patient management, then is either test, measured separately, equally effective in patient management?

Over the past 40 years, several studies were published that demonstrated that the DLNO (or TLNO in European terminology) had several advantages over the DLCO. The purpose of this paper is to show the reader the technical/physiological advantages of measuring DLNO compared to DLCO. Furthermore, we will attempt to convince the reader that because of these technical/physiological advantages, the DLNO is a better measure of gas transfer compared to the DLCO and thus can replace the DLCO test in pulmonary function laboratories. We argue that a patient's management of his/her pulmonary disease can be done equally well with DLNO compared to the DLCO and suggest that the DLNO test is the pulmonary function test of the future. There are a various situations where the DLNO test technically and physiologically differs in a substantial way from DLCO test. We will discuss these situations one by one, pointing out the differences and similarities of DLNO compared to DLCO.

2. Conceptual difference between DLNO and DLCO

The uptake of NO molecules from alveolar sacs to the haemoglobin compasses the following steps: passing through the alveolar cell wall, followed by passing through the layer of interstitium, then moving through a layer of endothelial cells, then followed by crossing the plasma, and then crossing the red cell membrane, and finally followed by binding to the Hb molecule near the inner surface of the red cell. As the reactivity of NO with Hb is high, no NO molecule can penetrate the red cell in its depth. The DLNO differs from the DLCO in an important factor, that is, the binding of NO to the Hb is much faster (approximately 1500 times faster) than the binding of CO to Hb (Gibson and Roughton, 1957). Due to this relatively slow binding, the chief barrier to CO uptake is within the red cell (~70–80%), and ~25% remaining resistance to CO diffusion is located in the alveolar-capillary membrane (Fig. 1A). In contrast, ~60% of the resistance for NO diffusion is within the alveolar-capillary membrane, while ~40% is within the red cell interior (Fig. 1A). Therefore, the DLNO is a better representative of the diffusive properties of the alveolar-capillary membrane than the DLCO (Hughes and van der Lee, 2013).

3. Diffusion dependency on alveolar volume

The relationship between the diffusion capacity and lung volume is very complex, in which three distinct associations play an important role:

3.1. DLCO versus alveolar volume

The DLCO decreases with voluntary lowering of lung volume at a given breath-hold time (Stam et al., 1991). The DLCO per unit of alveolar volume (DLCO/VA ≈ KCO) increases exponentially when lung volume is lowered, as in voluntary incomplete lung expansion, or in an "extrapulmonary ïestrictive disease (neuromuscular disease, chest stiffness or congenital abnormality, Fig. 2). The reason for this phenomenon is the volume to surface area ratio of the lung. We can imagine a simplified model of the lung volume (ignoring the dead space volume and the conducting airways), in which the lung volume equals the total number of alveoli times the mean vol-

[1] NO has a ~200 fold higher reaction velocity to hemoglobin compared to CO (Johnson et al., 1996).

[2] The "transfer factor of the lung for nitric oxide" (TLNO) was European terminology. It is equivalent to the North American terminology "pulmonary diffusing capacity of the lung for nitric oxide" (DLNO). The TLNO = DLNO when expressed in the same units.

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