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Review

Simultaneous measurement of pulmonary diffusing capacity for carbon monoxide and nitric oxide

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ABSTRACT

In Europe and America, the newly-developed, simultaneous measurement of diffusing capacity for CO (D_{LCO}) and NO (D_{LNO}) has replaced the classic D_{LCO} measurement for detecting the pathophysiological abnormalities in the acinar regions. However, simultaneous measurement of D_{LCO} and D_{LNO} is currently not used by Japanese physicians. To encourage the use of D_{LNO} in Japan, the authors reviewed aspects of simultaneously-estimated D_{LCO} and D_{LNO} from previously published manuscripts. The simultaneous D_{LCO}-D_{LNO} technique identifies the alveolocapillary membrane-related diffusing capacity (membrane component, D_M) and the blood volume in pulmonary microcirculation (V_C); V_C is the principal factor constituting the blood component of diffusing capacity (D_B, $D_B = \theta \cdot V_C$ where θ is the specific gas conductance for CO or NO in the blood). As the association velocity of NO with hemoglobin (Hb) is fast and the affinity of NO with Hb is high in comparison with those of CO, θ_{NO} can be taken as an invariable simply determined by

Abbreviations: A, alveolar gas; BHT, breath-holding time (sec); CF, cystic fibrosis; d, diffusivity of the gas (cm^2/s); D_{app}, overall apparent diffusing capacity for the gas neglecting the effects of functional inhomogeneities (mL/min/mmHg); D_B, blood component of diffusing capacity for the gas (mL/min/mmHg); D_L, diffusing capacity for the gas (mL/min/mmHg); D_L/V_A,, diffusing capacity per unit alveolar volume (rate constant of alveolar gas uptake per unit pressure, mL/min/mmHg/L); D_M, membrane component of diffusing capacity for the gas (mL/min/mmHg); DPLD, diffuse parenchymal lung diseases; Hb, hemoglobin; HbO_2, oxyhemoglobin; He, helium; I, inspired gas; K, Krogh factor for the gas (calculated as $S/(P_B–P_{H2O})$ and equal to D_L/V_A); MW, molecular weight (g/moL); PAH, pulmonary arterial hypertension; PAO_2, mean alveolar PO_2 (surrogate of mean capillary PO_2, mmHg); P_B, barometric pressure (mmHg); P_C, partial pressure of the gas in alveolar capillary (mmHg); P_{H20}, vapor pressure at body temperature (mmHg); S, slope of alveolar gas uptake during breath-holding; T_L, transfer factor (equal to D_L); T_L/V_A, transfer coefficient (equal to D_L/V_A); V_A, alveolar gas volume (L); V_{AT}, inspired or expired alveolar tidal volume (L); V_C, alveolar capillary blood volume (mL); V_D, anatomical dead space (mL); V_I, inspired gas volume (L); α, Bunsen solubility coefficient of the gas (mL/mL/atm); θ, specific gas conductance in blood (mL/min/mmHg/mL); $Y_{X/Y}$, relative Krogh diffusion constant of gas X against gas Y ($(\alpha \cdot d)_X/(\alpha \cdot d)_Y$); ω, ratio of permeability of erythrocyte membrane to that of erythrocyte interior

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Specific gas conductance
Blood volume

diffusion limitation inside the erythrocyte. This means that θ_{NO} is independent of the partial pressure of oxygen (PO_2). However, θ_{CO} involves the limitations by diffusion and chemical reaction elicited by the erythrocyte, resulting in θ_{CO} to be a PO_2-dependent variable. Furthermore, D_{LCO} is determined primarily by D_B (~77%), while D_{LNO} is determined equally by D_M (~55%) and D_B (~45%). This suggests that D_{LCO} is more sensitive for detecting microvascular diseases, while D_{LNO} can equally identify alveolocapillary membrane and microcirculatory abnormalities.

Contents

1. Historical backgrounds on lung diffusing capacity

In Europe and North America, the measurement of the diffusing capacity (D_L) for nitric oxide (NO) is used in a variety of lung diseases to evaluate the impediment of gas transfer in the acinus across the alveolocapillary membrane and microcirculation [1–6]. The use of NO diffusing capacity (D_{LNO}) required that the Task Force Panel organized by the European Respiratory Society (ERS) create standards for the measurement and interpretation of D_{LNO} [7]. To encourage the use of D_{LNO} in Japan, the authors have comprehensively reviewed the methodological and pathophysiological aspects of clinically using D_{LNO}.

It has been over 100 years since Marie Krogh developed the method to measure the single-breath carbon monoxide (CO) uptake through the alveolocapillary membrane [8]. Since then, the single-breath CO diffusing capacity (D_{LCO}) has become the most clinically useful pulmonary function test after spirometry and the measurement of lung volumes. A practical method to examine the single-breath D_{LCO} was proposed by Ogilvie et al. [9], and at the same time, Roughton and Forster [10] proposed a memorable model describing the gas transfer in the lung. They assumed that two processes could explain the transfer of CO from the alveolocapillary membrane to hemoglobin (Hb) in erythrocytes: (1) the membrane diffusing capacity for CO (D_{MCO}) and (2) the blood diffusing capacity for CO (D_{BCO}). The D_{MCO} reflects the diffusion limitation across the effective alveolocapillary membrane, which consists of gas-phase diffusion (if any), the alveolar wall, and the plasma layer surrounding the erythrocyte. The D_{BCO} is defined as the product of alveolar capillary blood volume (V_C) and specific gas conductance for CO in the blood (θ_{CO}). The θ_{CO} signifies the diffusive process across the membrane of the erythrocyte and its interior and incorporates the competitive, replacement reaction of CO with oxyhemoglobin (HbO_2). Since the reciprocals of D_{MCO} and D_{BCO} are the gas-transfer resistances that are connected in series, the total resistance for CO transfer, $1/D_{LCO}$, is expressed as:

$$1/D_{LCO} = 1/D_{MCO} + 1/(\theta_{CO} \cdot V_C) \quad (1)$$

Roughton and Forster [10] developed a clever method for determining D_{MCO} and V_C from D_{LCO} measured at two different alveolar partial pressure of oxygen (alveolar PO_2) (classic two-step alveolar PO_2 technique).