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Pathophysiological advantages derived from simultaneous measurement of diffusing capacity for carbon monoxide (DLCO) and nitric oxide (DLNO)

It has been over 100 years since Marie Krogh developed the method to measure the transfer of carbon monoxide (CO) through the alveolar wall. 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. In 1957, Roughton and Forster established a model in which the two processes for explaining the transfer of CO from alveolar gas phase to hemoglobin (Hb) in erythrocytes were assumed, i.e., the membrane diffusing capacity for CO (D_{MCO}) and the blood diffusing capacity for CO (D_{BCO}). The D_{MCO} reflects the process of CO diffusion across the effective alveolocapillary membrane, which consists of the alveolar gas phase, the alveolocapillary tissue barrier, and the plasma layer surrounding the erythrocyte (Fig. 1). 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 erythrocyte (membrane and its interior) and incorporates the competitive, replacement reaction of CO with oxyhemoglobin (HbO_2) in the erythrocyte. The replacement reaction between CO and HbO_2 is significantly influenced by capillary PO_2.

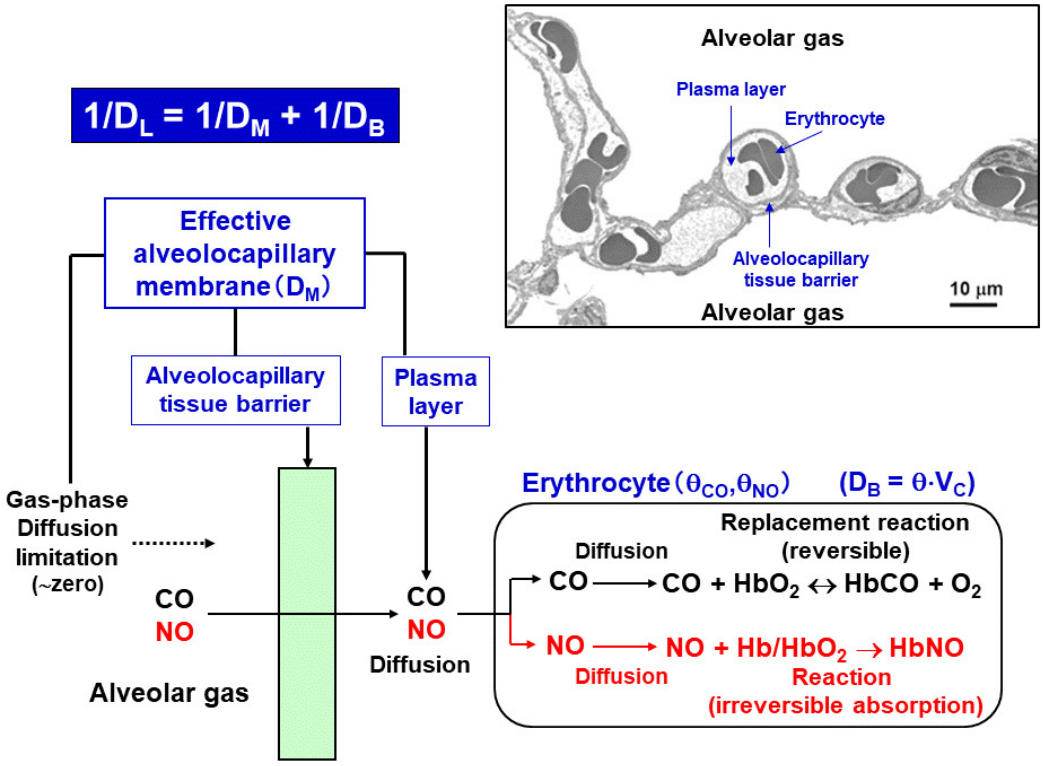

Fig. 1. Schematic presentation of CO and NO transfer from alveolar gas to erythrocyte.

In the late 1980s, Guénard and Borland independently developed a novel method of simultaneously measuring D_{LCO} and D_{LNO}. Like D_{LCO}, D_{LNO} is composed of D_{MNO} and D_{BNO} ($\theta_{NO} \times V_C$). However, the transfer characteristics of NO through the alveolar wall, including the alveolocapillary membrane and the pulmonary capillary-network, differ substantially from those of CO. NO is more diffusible than CO in the aqueous media, including the alveolocapillary membrane, the plasma layer, and the inside of the erythrocyte. Furthermore, the association velocity of NO with Hb is conspicuously faster than that of CO and the affinity of NO with Hb is tremendously higher than that of CO, suggesting that the chemical reaction of NO with Hb does not impede the erythrocyte NO transfer. Thus, one can consider that the CO transfer through the alveolar wall is limited both by diffusion and reaction, but the NO transfer is primarily prescribed by diffusion. Consequently, D_{LCO} and D_{LNO} reach about 30 mL/min/mmHg and 140 mL/min/mmHg in normal adults, respectively ($D_{LNO}/D_{LCO} \simeq 4.8$). Furthermore, the relative contribution of the resistance for CO imposed by the effective alveolocapillary membrane ($1/D_{MCO}$) and that by the erythrocyte ($1/D_{BCO}$) to the total resistance of CO transfer ($1/D_{LCO}$) are 23% and 77%, respectively (Fig. 2). On the other hand, the relative contribution of $1/D_{MNO}$ and that of $1/D_{BNO}$ to $1/D_{LNO}$ are 55% and 45%, respectively. These facts indicate that D_{LCO}-associated parameters have a high sensitivity for detecting pulmonary capillary damage, while D_{LNO}-associated parameters equally detect alveolocapillary membrane damage and pulmonary capillary damage. As such, the simultaneous measurement of D_{LCO} and D_{LNO} improves the diagnostic precision of identifying pathological changes located in the alveolar wall.

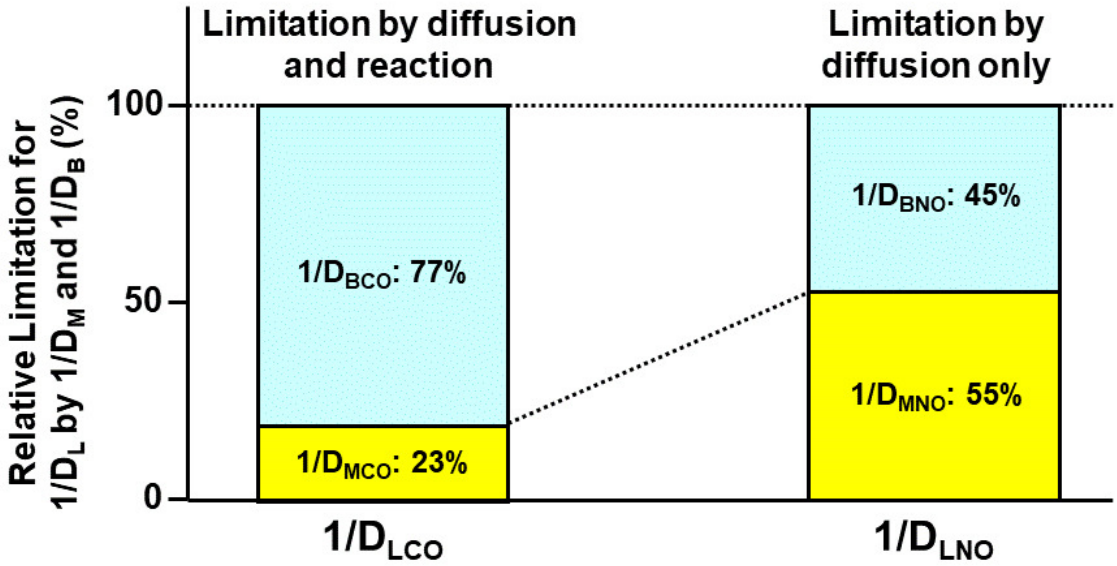

Fig. 2. Relative contribution of 1/DM and 1/DB to overall resistance of 1/DL.

For estimating D_M and V_C, two consecutive measurements at different alveolar PO_2 are required when the classical D_{LCO} method is applied, but only one measurement is sufficient when D_{LCO} and D_{LNO} are simultaneously measured. This fact indicates that the simultaneous measurement of D_{LCO} and D_{LNO} is more

convenient clinically and reduces the time required for determining the D_M and V_C. The D_M/V_C is a clinically important parameter because it changes sensitively depending on the pathological condition of the alveolocapillary membrane and that of the pulmonary capillary-network. The D_M/V_C is expected to decrease by a lung disease predominantly affecting the alveolocapillary membrane (for instance, idiopathic pulmonary fibrosis and non-specific interstitial pneumonia) but to increase by a lung disease preferentially injuring the pulmonary microcirculation (for instance, idiopathic pulmonary arterial hypertension and microvascular angiitis).

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