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Theoretical analysis of the determinants of lung oxygen diffusing capacity

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HIGHLIGHTS

- The process of pulmonary oxygen uptake is analyzed using a theoretical model.
- Lung diffusing capacity is expressed in terms of hematocrit and capillary diameter.
- The predicted diffusing capacity is significantly lower than previous estimates.
- The predicted diffusing capacity is higher than that suggested by experimental data.
- This discrepancy may reflect heterogeneity of perfusion and ventilation in the lung.

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ABSTRACT

The process of pulmonary oxygen uptake is analyzed to obtain an explicit equation for lung oxygen diffusing capacity in terms of hematocrit and pulmonary capillary diameter. An axisymmetric model with discrete cylindrical erythrocytes is used to represent radial diffusion of oxygen from alveoli through the alveolar–capillary membrane into pulmonary capillaries, through the plasma, and into erythrocytes. Analysis of unsteady diffusion due to the passage of the erythrocytes shows that transport of oxygen through the alveolar–capillary membrane occurs mainly in the regions adjacent to erythrocytes, and that oxygen transport through regions adjacent to plasma gaps can be neglected. The model leads to an explicit formula for diffusing capacity as a function of geometric and oxygen transport parameters. For normal hematocrit and a capillary diameter of 6.75 μm, the predicted diffusing capacity is 102 ml O_2 min^{-1} $mmHg^{-1}$. This value is 30–40% lower than values estimated previously by the morphometric method, which considers the total membrane area and the specific uptake rate of erythrocytes. Diffusing capacity is shown to increase with increasing hematocrit and decrease with increasing capillary diameter and increasing thickness of the membrane. Simulations of pulmonary oxygen uptake in humans under conditions of exercise or hypoxia based show closer agreement with experimental data than previous models, but still overestimate oxygen uptake. The remaining discrepancy may reflect effects of heterogeneity of perfusion and ventilation in the lung.

1. Introduction

The rate of oxygen uptake from the lung into the bloodstream is a critical determinant of functional capacity and is of paramount importance under normal conditions (including exercise) as well as in disease. The rate at which oxygen is taken up by erythrocytes in pulmonary capillaries is termed lung diffusing capacity, and is affected by several geometric and functional factors. The diffusing capacity of the lung is higher than would be necessary to meet the needs of healthy individuals at rest under normoxic conditions, but can become limiting under conditions of exercise, hypoxia, or disease. Such impairment of oxygen uptake can lead to inadequate oxygen delivery, with consequences that range from short-term dependence on anaerobic metabolism to organ failure and death. The lung diffusing capacity is therefore a crucial parameter in the analysis of oxygen transport in the body under a range of physiological and pathological conditions. The main physical processes determining lung diffusing capacity are well known, and a number of theoretical models have been developed, as discussed below. However, existing methods for estimating this parameter give widely varying results, and may not be suitable for examining the effects of hemodynamic or structural changes

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occurring in the lung. There is a need for a model of lung diffusing capacity that takes into account such changes but is simple enough to be used as a component in multi-organ simulations.

The objective of this study is to estimate lung diffusing capacity by analyzing the fundamental processes of pulmonary oxygen transport, and to use this result to predict the rate of oxygen uptake under physiological stress (exercise and hypoxia). Lung diffusing capacity (D_{LO_2}) is generally defined via

$$\dot{V}_{O_2} = D_{LO_2} \cdot (P_A - \overline{P_b}) \tag{1}$$

where $\dot{V}_{O_2}$ is the oxygen consumption rate, P_A is the partial pressure of oxygen (P_{O_2}) in alveolar air and $\overline{P_b}$ is the mean P_{O_2} in pulmonary capillary erythrocytes (Weibel, 1999). In this definition, D_{LO_2} depends on the geometry of the lung and the diffusive mass transfer properties of the alveolar–capillary membrane, plasma, and erythrocytes, but is independent of blood flow rate, ventilation, and oxygen flux.

As blood traverses capillaries in the lung, P_b varies nonlinearly, such that $\overline{P_b}$ cannot be deduced directly from measurable parameters such as arterial and venous P_{O_2} (P_a and P_v). Therefore, D_{LO_2} cannot be directly estimated from experimental data. For this reason, Foucquier et al. (2013) proposed an alternative definition of diffusing capacity D'_{LO_2} in terms of venous P_{O_2}:

$$\dot{V}_{O_2} = D'_{LO_2} \cdot (P_A - P_v) \tag{2}$$

This effective mass transfer coefficient includes effects of the variation of P_b during transit through the lung as well as effects of heterogeneity of blood flow, alveolar geometry, etc. In blood traversing the lung, the P_{O_2} approaches alveolar P_{O_2}, implying that $|P_A - \overline{P_b}| \le |P_A - P_v|$. Hence, the lung diffusing capacity D_{LO_2} provides an upper bound on the effective diffusing capacity D'_{LO_2}.

As already noted, knowledge of D_{LO_2} is important for the quantitative understanding of oxygen transport in the lung. Since D_{LO_2} is not directly measurable, several previous studies have used theoretical approaches to obtain estimates (see Table 1), as briefly reviewed here.

The morphometric method (Weibel, 1999, 2009; Weibel et al., 2005) is based on the concept (Roughton and Forster, 1957) that resistance to oxygen diffusion can be represented as two components in series, one associated with the alveolar membrane (D_{MO_2}) and one associated with erythrocytes (D_{eO_2}):

$$(D_{LO_2})^{-1} = (D_{MO_2})^{-1} + (D_{eO_2})^{-1} \tag{3}$$

Blood is treated as a continuum and the entire membrane participates in gas exchange. The membrane component is estimated as

$$D_{MO_2} = K_{O_2} \cdot \frac{(1/2)[S(A) + S(c)]}{\tau_{hb}} \tag{4}$$

where K_{O_2} represents the Krogh diffusion constant, $(1/2)[S(A)+S(c)]$ represents the average of the alveolar surface area $S(A)$ and the capillary surface area $S(c)$ (approximately 130 m^2 in humans), and τ_{hb} represents the harmonic mean of the distance between the alveolar surface and the erythrocyte surface (approximately 1 μm), which includes both the plasma and alveolar–capillary membrane compartments (Weibel et al., 1993). The erythrocyte component is calculated from

$$D_{eO_2} = \theta_{O_2} \cdot V(c) \tag{5}$$

where $V(c)$ represents pulmonary capillary blood volume (approximately 194 ml) and θ_{O_2} represents the oxygen unloading conductance of blood (i.e. the reaction rate of oxygen with whole blood), about 1.8 ml O_2 ml^{-1} min^{-1} $mmHg^{-1}$ (Weibel, 1999). This approach yields D_{LO_2} = 158 ml O_2 min^{-1} $mmHg^{-1}$ in humans (Weibel, 1999), independent of hematocrit (Weibel et al., 1993).

This estimate far exceeds observed diffusing capacity values for humans at rest and during exercise, which are approximately 20–60 ml O_2 min^{-1} $mmHg^{-1}$ (Hsia, 2002; Hughes and Bates, 2003). Awareness of this discrepancy has motivated a number of modifications to the morphometric method and development of alternative approaches. A reexamination of the morphometric method (Crapo and Crapo, 1983; Crapo et al., 1988) concluded that Eq. (3) should be modified by including correction factors in each term to accurately represent pulmonary oxygen transport. Subsequently, the model was modified by Weibel et al. (1993) to incorporate effects of the plasma layer as well as hematocrit dependence, with a resulting ~30% reduction in predicted D_{MO_2}.

The particulate nature of blood significantly affects intraluminal diffusion resistance (Hellums, 1977; Hellums et al., 1996). In order to account for this effect, several theoretical studies of oxygen transport from alveoli to discrete erythrocytes in the pulmonary capillaries have utilized finite element models, and have variously accounted for plasma convection between erythrocytes, the reaction rate of hemoglobin with oxygen within the erythrocyte, erythrocyte shape, and a fluid barrier (Federspiel, 1989; Fink, 2002; Foucquier et al., 2013; Hsia et al., 1995, 1997, 1999; Reynolds et al., 2010; Sharan et al., 1991; Singh et al., 1980; Whiteley, 2006; Whiteley et al., 2001, 2003).

The model of Federspiel (Federspiel, 1989; Federspiel and Popel, 1986) considers spherical erythrocytes surrounded by plasma within a cylindrical capillary and an annular layer of tissue representing the alveolar–capillary membrane. This model incorporates the kinetics of oxyhemoglobin binding and predicts a decrease in diffusing capacity with increasing intercell spacing (decreasing hematocrit) due to a lower relative radial flux at the plasma gaps. The resulting estimate of D_{LO_2} is comparable to that obtained by the morphometric method (Table 1). Frank et al. (1997) use a similar approach but with axisymmetric parachute-shaped erythrocytes, and obtain estimates of D_{LO_2} of similar magnitude. Simulations by Hsia et al. (1995, 1997) of carbon monoxide diffusion in two dimensions with circular or parachute-shaped erythrocyte shapes similarly show a strong dependence of diffusing capacity on cell spacing.

In summary, previous analyses of lung diffusing capacity considering discrete erythrocytes have successfully addressed the limitation of the morphometric model with respect to dependence on hematocrit, but the discrepancy between predicted D_{LO_2} and observed diffusing capacities in humans remains unresolved. Therefore, we here develop a simple theoretical model for pulmonary oxygen uptake, taking into account the particulate nature

Table 1
Previous theoretical estimates of D_{LO_2} and D_{MO_2} (ml O_2 min^{-1} $mmHg^{-1}$).

Authors	D_{MO_2}	D_{LO_2}	Notes
Gehr et al. (1978)	553–586	125–263	Morphometric method
Weibel et al. (2005)	350	158	Morphometric method
Federspiel (1989)		135	Discrete spherical erythrocytes (H_D=0.237)
Frank et al. (1997)	112–199	93–185	Axisymmetric, parachute erythrocytes; $D_{RBC} = 2.4 \times 10^{-5}$ cm^2/s, blood volume 162.8 ml
Foucquier et al. (2013)	86–145		Biconcave erythrocytes (H_D=0.45)