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Review Article

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Computer Models on Oxygenation Process in the Pulmonary Circulation by Gas Diffusion

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Abstract

In this article we introduce computer models that have been developed in the past to determine the concentration of metabolic gases, the oxygen and carbon dioxide, along the pulmonary circulation. The terminal concentration of these gases in the arterial blood is related with the total change of the partial pressure of the same gases in the alveoli for the time beginning with inspiration and ending with expiration. It is affected not only by the ventilation-perfusion ratio and the gas diffusion capacity of the lung membrane but also by the pulmonary defect such as shunt, dead space, diffusion impairment and ventilation-perfusion mismatch. Some pathological pulmonary symptoms such as ARDS and CDPD can be understood through the mathematical models of these pulmonary dysfunctions. Quantitative study on the blood oxygenation process using various computer models is therefore of foremost importance in order to monitor not only the pulmonary health but also the cardiac output and cell metabolism. Reviewed in this paper include the basic and advanced methods that enable numerical study on the gas exchange and on the arterial oxygenation process, which might depend on the various heart and lung physiological conditions listed above.

Keywords: computer models, pulmonary circulation, gas diffusion

Introduction

Breathing is made by the movement of the thoracic diaphragm and contraction of the respiration muscles by which the elastic lung is forced to expand and shrink periodically. The negative pleural pressure in the thoracic cavity, that holds the lung inflated in the thoracic cage, fluctuates in average between -5 and -7.5 *cm* of waters in the normal respiration. Alveolar pressure varies, in turn, from +1 *cm* of water in expiration and -1 *cm*of water in inspiration. The difference between the pleural and alveolar pressures is called the transpulmonary pressure. Compliance is the index of lung elasticity which is in average about 200 *mililiters* of air per *cm*of water of transpulmonary pressure. Atmospheric air moves into the lung when the alveolar pressure is negative; when it is positive, the alveolar gas with high carbon dioxide content is expelled.

Oxygen in the alveolar air is absorbed by the pulmonary capillary blood via the alveolar membrane and interstitial tissues. In reverse, the carbon dioxide is drained from the capillary blood to the alveolar gas in the opposite direction. Molecular diffusion is purely responsible for the gas exchange between the alveolar air and the capillary blood. Diffusion of a gas is activated in the direction of negative gradient of the partial pressure (or concentration), namely from the higher partial-pressure tissue(or concentration) to the lower one (or concentration). Diffusion of gas molecules is a very fast and efficient means of material transport in the alveolar membrane consisting of membrane epithelial cells, interstitial tissue cells, endothelial cells of capillary wall, and blood cells plus plasma.

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The oxygen molecules transported by diffusion from the alveoli to the pulmonary capillary are chemically combined with the hemoglobin in the red blood cell. This oxygenated blood is, in turn, pumped to the body tissues by the mechanical energy of the left heart in the systemic circulation. The carbon dioxide molecules are produced in the somatic tissues when the oxygen is consumed for cell metabolism; they are collected to the capillaries and veins, where they are combined with the hemoglobin and other proteins, before transported to the mixed veins; the venous blood is, in turn, pumped to the pulmonary circulation by the mechanical energy of the right heart. In the pulmonary capillaries, the carbon dioxide molecules are drained to the alveolar gas by diffusion along the negative gradient of concentration.

The partial pressure of oxygen in the alveolar air and the diffusion capacity of the lung dictate how much oxygen molecules to be dissolved for transport to the capillary blood. The low partial pressure of the carbon dioxide in the alveolar air, onthe other hand, plays the role of diffusion pump, draining the carbon dioxide molecules from the capillary blood to the alveolar air. Given a lung, the concentration or saturation of hemoglobin with a particular gas in the pulmonary oxygenation is dependent on the partial pressure of the gas in the alveoli plus the diffusion capacity of the lung; it is depicted by the so called dissociation curve of the gas.

Individual alveolus may have slightly different gas exchange capacity but the lung as a mass ofthe whole alveoli would exhibit, in statistical average, a definite dissociation curve. On this reason, we can make a physiological modeling using a single alveolus that has the average gas exchange capacity of the human lung. A set of Fick's law on gas diffusion plus mass balanceequations for different gases is appropriate to quantitatively describe the gas exchange between the alveolus and the capillary as a function of the ventilation-perfusion ratio and the gas diffusion capacity. Since they are implicit and nonlinear equations, we need special computer algorithms for numerical solution.

Earlier methods include the works by Riley & Cournand,[1] Rahn[2] and Rahn & Fenn.[3] They have been extended to the later numerical methods by Kelman,[4] Olszowka & Farhi[5] and West[6] which modified the graphic approach known as O2-CO2 diagram; see Rahn & Fenn.[3] Additional papers appeared to show how to predict the concentration of oxygen and carbon dioxide in the blood, associated with the saturation of hemoglobin in the red blood cell(Kelman,[7] Severinghaus[8]) that depends on the gas partial pressure(Kelman,[9] Loeppky[10]). A numerical study has also appeared on the gas diffusion capacity which is associated with the physiological property of the alveolar membrane[11]. The numerical and theoretical studies by Piiper[12], Vidal Melo et al.[13-15] and Loeppky et al.[16] investigated the respiratory disease ARDS(adult respiratory distress syndrome) and COPD(chronic obstructive pulmonary disease) using the models of pulmonary diffusion impairment with ventilation-perfusion ratio mismatch. In this article, we review some of those basic and advanced methods that have availed numerical study on blood oxygenation by the gas exchange between alveolar air and pulmonary capillary blood in normal respiration.

Ventilation-Perfusion Ratio

Oxygenation of blood in the pulmonary circulation, from the mixed vein to the end capillary, is the result of gas exchange between the alveolar air and the pulmonary capillaries. Gas exchange is made by diffusion of oxygen and carbon dioxide molecules, from the high molecular concentration to the lower concentration and through the alveolar membrane. If there is diffusion impairment or ventilation-perfusion mismatch on some reason during successive breaths, it could impede the oxygenation process or a respiratory failure could be resulted. It is therefore of foremost importance to know how blood will be oxygenated by the gas exchange under the influence of various factors (such as diffusion capacity of a lung, partial pressure of the gases in the alveolar air and in the mixed venous blood) and even with some cardiac and pulmonary deficiencies.

The oxygenation of blood in the pulmonary capillaries results in the change of partial pressures of oxygen and carbon dioxide in the alveolar air during the breath. The total pressure of the gas mixture, 760 *mmHg* at sea level average, is constant, which is equal to the sum of all the partial pressure of individual gases by Dalton's law. Concentration of oxygenin the blood is a nonlinear function of the partial pressures of oxygen and carbon dioxide in the alveoli. The equations (1)-(3) are

the mass balance equations and equation 2(4) is the Dalton's law. Since the nitrogen is inert in the oxygenation process, its partial pressure and concentration remains trivially constant in the pulmonary system.

$$(\dot{V}_I/\dot{Q})P_{I_{O2}} - (\dot{V}_A/\dot{Q})P_{A_{O2}} = k(C_{c'_{O2}} - C_{\bar{V}_{O2}}) \quad (1)$$

$$(\dot{V}_A/\dot{Q})P_{A_{CO2}} = k(C_{\bar{V}_{CO2}} - C_{c'_{CO2}}) \quad (2)$$

$$(\dot{V}_I/\dot{Q})P_{I_{N2}} - (\dot{V}_A/\dot{Q})P_{A_N} = \lambda_{N_2}(C_{c'_{N2}} - C_{\bar{V}_{N2}}) \quad (3)$$

$$P_{A_{O2}} + P_{A_{CO2}} + P_{A_{N2}} = P_B - P_{H_2O} \quad (4)$$

Here, $\dot{V}_I$ is the inspired air per unit time(liters/min); $\dot{V}_A$ is the alveolar ventilation; $\dot{Q}$ is the perfusion of blood; P is partial pressure of the gas, C is the concentriation of the gas in the blood; P_{H2O} is the vapour pressure in the lung, equal to 47.0 mmHg.

Among the subscripts, I denotes the inhaled air. Among the subscripts, I denotes the inhaled air, A the alveoli, C' the end capillary, $\bar{V}$ the mixed venous, and B indicates the barometric or atmospheric. Among the constants, λ(=0.0017)is the blood to gas partition coefficient for the nitrogen[17] and k is a constant making the units consistent, keeping the convention that gas concentrations are expressed at STPD(standard temperature and pressure, dry) while ventilation volumes are expressed at BTPS(body temperature and pressure saturated with water vapor). This constant is given by

$$k = 760(Temp + 273)/273 \quad (5)$$

when the body temperature 37 is used to evaluate the variable *Temp*, it becomes . k =863.

To begin with, we suppose that the concentrations of oxygen and carbon dioxide in the mixed venous blood are known. Then the ventilation-perfusion ratio, $\dot{V}_A/\dot{Q}$, can be determined by the equation system (1) to (4). The first two equations are coupled through the unknown ventilation-perfusion ratio. They are also nonlinear since diffusion is not a linear function of the partial pressures, as can be verified from the dissociation curves of oxygen and carbon dioxide. To solve the first two equations, we need a little cumbersome, iterative calculation procedure.

We first obtain the variable $\dot{V}_I/\dot{Q}$ from the equation (3), and the partial pressure P_{A_N} from (4); we then substitute them into equation (1). The resultant modified equation is then divided by equation (2). Here we neglect nitrogen exchange since this gas is inert and remains constant in the blood. Then we obtain the expression for the gas exchange R in two forms, from the left and right hand side of the resultant equation. They are given by equations (6) and (7).

$$R = \frac{P_{A_{CO2}}(1 - F_{I_{O2}})}{(P_{I_{O2}} - F_{I_{O2}}P_{A_{CO2}} - P_{A_{CO2}})} \quad (6)$$

$$R = \frac{(C_{\bar{V}_{CO2}} - C_{C'_{CO2}})}{(C_{C'_{O2}} - C_{\bar{V}_{O2}})} \quad (7)$$

Here, $F_{I_{CO2}}$ is the fraction of the oxygen partial pressure in the atmospheric air. In the lung if there is no diffusion failure, the oxygen and the carbon dioxide in the alveoli have the same partial pressures as those in the pulmonary end-capillary blood, that is, and $P_{A_{O2}} = P_{C'_{O2}}$ $P_{A_{CO2}} = P_{C'_{CO2}}$Eliminating the alveolar-gas partial pressures in terms of the end-capillary gas concentrations from equations (6) and (7) and using

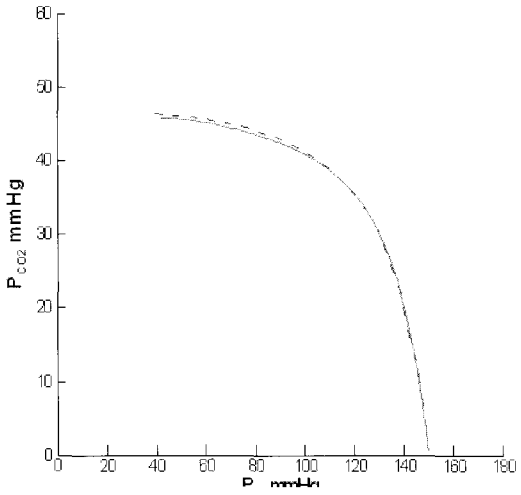

Figure 1. O_2-CO_2 diagram showing the possible pair of oxygen and carbon dioxide concentrations as the ventilation-perfusion ratio is changed along the pulmonary capillary by the gas exchange, reproduced using Kelman's method (1968).4 Used data: Fio_2 = 21%, Hb=14.8g%, Hcrit=45%, Cvo_2 = 15ml/100ml, $Cvco_2$=52ml/100ml, N2 exchange is ignored.

equation (2) at the same time, wefinally have the expression for the ventilation-perfusion ratio ($\dot{V}_I / \dot{Q}$). By varying the value of ($\dot{V}_I / \dot{Q}$), a conventional oxygen-carbon dioxide curve is obtained as in Fig. 2. From this curve, the concentrations of oxygen and carbon dioxide can be calculated by Kelman method.[7,4,9]

Numerical Methods for the Gas Diffusion Capacity

Many equations have been developed to model the diffusion capacity of oxygen in the lung since Christian Bohr[18] first introduced a method of calculating diffusion of oxygen in the pulmonary capillaries using Fick's equations. In these methods the oxygen diffusion capacity is evaluated by calculating the change of concentration of oxygen in the blood from the mixed vein to the end capillary. In the beginning there have not been many reports on the diffusion of carbon dioxide and its interaction with the oxygen. Riley and Cournand.[19,20] investigated the relation between the diffusion impairment and the ventilation-perfusion ratio using Bohr's method. Ignored in their paper are, however, the amount of oxygen dissolved in the blood and the chemical reaction of the oxygen with the hemoglobin in the red blood cell. Roughton and Forster[21] indicated the importance of chemical reaction rate in the diffusion process; they explained the effect of many variables such as the chemical reaction rate, the volume of the capillary blood vessel, and the diffusion capacity of the alveolar membrane. Staub et al.[22,24] measured the chemical reaction rate with different saturation of oxygen to apply the Bohr's method. Piiper et al.[25,26,12] presented a few models to relate the diffusion-perfusion impairment to the ventilation-perfusion impairment. However, they failed to take into account the effect of chemical reaction rate and the dissociation curves of oxygen and carbon dioxide.

Wagner and West[27] introduced a model in order to study the diffusion of gases in alung under different values of ventilation-perfusion ratio. In their work, they calculated total diffusion of the oxygen and the carbon dioxide in the blood between the mixed vein and the pulmonary end capillary, by considering the chemical reaction rate of the gas against the blood and the amount of oxygen dissolved in the blood. They also considered in the model the interaction of oxygen and carbon dioxide via independent dissociation curves. Vidal Melo et al.[14,15]

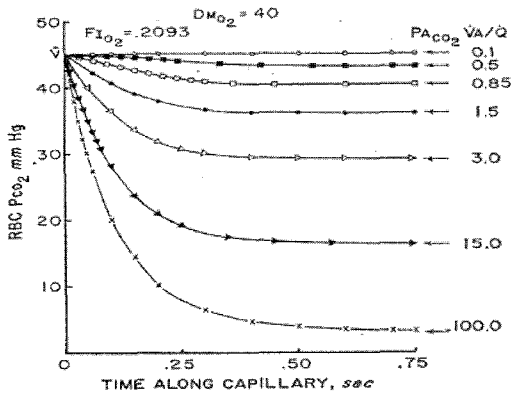

Figure 2. Alveolar O_2 partial pressure along the time course, from Wagner and West[27]; $D_{M_{O_2}}$ is the membrane diffusion capacity.

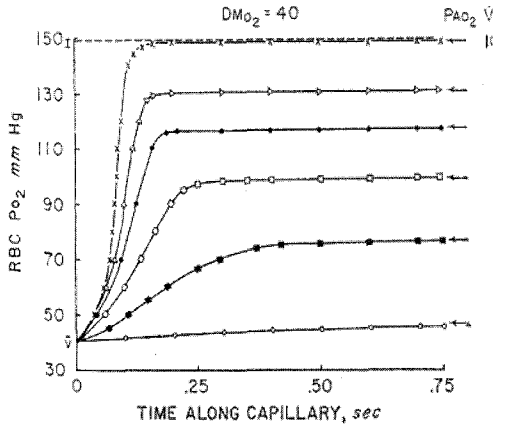

Figure 3. Alveolar CO_2 partial pressure along the time course, from Wagner and West.[27] $D_{M_{O_2}}$ is the membrane diffusion capacity

used the method of Wagner and West[27] to analyze the diffusion impairment with the ventilation-perfusion mismatch in the lung.

Derivation of Equations for the Gas Diffusion Capacity

The gas diffusion capacity is the volume of gas exchange by pulmonary diffusion, drivenby the unit difference(1 mmHg) of time-averaged partial pressure between the alveoli and the pulmonary capillary:

$$D_L = \frac{\dot{V}_A}{(P_A - P_C)} \tag{8}$$

D_L : diffusion capacity [ml/min/mmHg]
$\dot{V}_A$: gas volume consumed by diffusion in the alveoli
P_A : mean partial pressure in the alveoli
P_C : mean partial pressure in the capillaryblood

Diffusion of a gas through the alveolar membrane is due to the gradient of the number density of the gas molecules distributed in the alveolar air and in the pulmonary interstitial tissues. This gradient is, of course, resulted from the different partial pressures of the gas between the alveoli and the capillary. To determine the oxygen diffusion capacity, for example, we must know the time-averaged oxygen concentration in the capillary and the time-averaged partial pressure of oxygen in the alveoli. Similarly, for the carbon dioxide, the time-averaged concentration in the capillary and the time-averaged partial pressure in the alveoli will determine the diffusion capacity of the carbon dioxide in the lung. For this purpose we modify equation (8) using the method of Wagner & West,[27] to get the oxygen concentration in the end capillary as

$$\frac{dC_{c'_{O2}}}{dt} = \frac{100}{V_C} D_{L_{O2}} (P_{A_{O2}} - P_{C_{O2}}) \qquad (9)$$

where D_{LO2} is the diffusion capacity of the whole lung and V_C is the total blood volume in the capillary network.

The volume of gas exchange can be determined as a function of the ventilation-perfusion ratio using the gas diffusion capacity of the lung. The calculation procedure is rather simple because the relations are linear first-order ordinary differential equations that can be integrated by the Runge-Kutta method along the gas exchanging capillary or in the respiration time. To guarantee a calculation accuracy, a close connection or interaction among the diffusion, ventilation and perfusion should be taken into account. Fig.2 and Fig.3 represent respectively the concentration curve of oxygen and carbon dioxide in the capillary blood, obtained by integrating equation (9) in time course, for five values of ventilation-perfusion ratio.

The Ventilation-Perfusion Ratio and the Gas Diffusion Capacity

The pulmonary dysfunction by limitation of oxygen diffusion and ventilation-perfusion ratio mismatch is illustrated in the following cases. (1) Increased alveoli and decreased partial pressure of oxygen in the pulmonary artery are observed in the young piglet less than 45 days after its birth that can breathe spontaneously. They seem to have been caused by diffusion impairment with ventilation-perfusion ratio mismatch. When the cardiac output is increased in a piglet under 4-week-old that can breathe by a mechanical ventilation, decrease in both the partial pressure of the oxygen and the specific diffusion capacity, $D/(Q\times\beta)$,have been observed, where D is the diffusion capacity, Q is the perfusion, and is the capacitance coefficient. When the cardiac output was decreased, an opposite result was obtained.[28] (2) Inappropriate balance between the diffusion and the perfusion is observed during the exercise of human. Examples are the ventilation-perfusion ratio mismatch[29]and the diffusion limitation.[30] (3) The cause of the ARDS(adult respiratory distress syndrome) and the DIPD(diffuse interstitial pulmonary disease) is not known; however, injury in the basic gas exchange mechanism such as decreased lung volume and increased shunt are suspected to be responsible.[31]

For example, it is reported that measurement of the carbon monoxide diffusion capacity from the ARDS patients, using the rebreathing method by Macnaughton and Evans[32] gives a very small value. The diffusion impairment observed from the data of several patients reveals that the ARDS is caused from the common residual defect of the lung function. The diffusion limitation with the ventilation-perfusion ratio mismatch might be a disease between the therapeutic step and the acute state. Piiper[12] investigated the relation between the ventilation-perfusion ratio $\dot{V}_A / \dot{Q}$ versus the specific diffusion capacity *D/Q*; he showed that $\dot{V}_A / \dot{Q}$ mismatch and *D/Q* distribution were in nonlinear interaction in order to determine the degree of oxygenation in the arterial blood. Piiper[33] further suggested a new model given by $\dot{V}_A / \dot{Q}$ $D/(Q\times\beta)$ and using a factor β .

Mathematical models aimed to evaluate the gas concentration in the arterial blood affected by the shunt have been developed by taking account of the ventilation-perfusion ratio and the diffusion limitation

separately. Miller et al.[34] and West[35], who the shunt in the blood, the dead space in the alveoli, the cardiac output, and the rate of gas particle diffusion through the alveolar membrane of variable thickness. ventilation-perfusion mismatch, observed that higher partial pressure of oxygen (Pao2) was obtained in the arterial blood as the perfusion is increased. Granger et al.[36] showed that partial pressure of oxygen was decreased when the physiologic shunt was increased; they assumed that the lung has a diffusion limitation uniformly constant. In their method, the diffusion was modeled by a linear dissociation curve(Fick's first law) with the assumption that oxygen concentration is low in the blood. In their paper, the alveolar air-capillary blood equilibrium is explained in terms of the specific diffusion capacity, $D/(Q\times\beta)$. However, they neglected to consider the oxygen-carbon dioxide interaction; they also failed to present a theoretical model for the diffusion limitation and ventilation-perfusion ratio, as a function of gas concentration in the arterial blood and cardiac output.

In order to evaluate the cardiac output that affects the partial pressure of oxygen in both the arterial blood and alveolus, the diffusion impairment with ventilation-perfusion ratio mismatch was modeled by Vidal Melo et al.[14,15] Using a schematic diagram shown in Fig.4, they explained the diffusion impairment with ventilation-perfusion mismatch in terms of the shunt in the blood, the dead space in the alveoli, the cardiac output, and the rate of gas particle diffusion through the alveolar membrane of variable thickness.

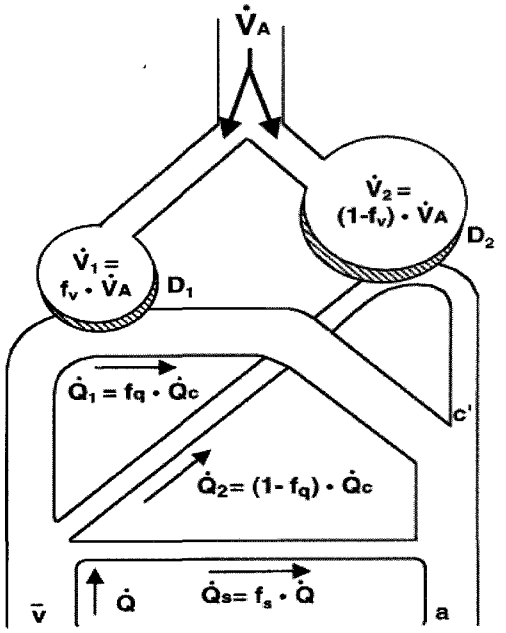

Figure 4. A schematic explaining diffusion impairment (i.e., diffusion capacities D1 ≠ D2) with ventilation-perfusion ratio mismatch (i.e., the perfusion the perfusion $\dot{Q}_1 \neq \dot{Q}_2$ from Vidal Melo.[15]

Conclusion

We have reviewed the basic mechanism and principles of human respiration. The exchange of gas through the alveolar membrane by molecular diffusion depends on the difference between the partialpressure of the gases in the alveoli and the concentration of the gases dissolved in the capillary blood. The conversion between the two variables when an equilibrium is reached depends on the physical and physiological lung capability called as the gas diffusion capacity. The pulmonary oxygenation can be negatively influenced by other factors like diffusion impairment with ventilation- perfusion mismatch. The gas exchange is mathematically modeled by various equations like Fick's equations, mass balance equations, and others. The numerical methods are basically iterative because the equations are nonlinear and mathematically coupled. In this article we have reviewed the basic and advanced methods for solution of the respiration model equations with discussion of the results.

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