A mathematical model for the first derivative wave analysis of the volumetric capnogram from the perspective of erythrocyte motion profiles

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ABSTRACT

Current trends in monitoring system are leading to the adoption of volumetric capnogram (Vcap). The first derivative wave analysis (FDWA) of Vcap represented the cardiogenic oscillations (CarO) as a propagated wave and the slope of phase III (SIII) as a constant. Until today the genesis of CarO and SIII is however under debate. In this study, we defined motion profiles of erythrocytes in the pulmonary parenchyma as pulsed-run and random-walk, on the basis of which we obtained a new mathematical expression describing FDWA of Vcap. The mathematical model of Vcap provided theoretical explanation concerned with motion profiles of erythrocytes about the genesis of CarO and SIII. As the results, the mathematical model predicted the close relationship between SIII and the transfer factor of carbon monoxide, which will be used for estimating validity of this mathematical model. In addition, the velocity of propagated wave in the phase III was suggested as a new physiological variable to estimate elastic properties of pulmonary arterioles, and a new measuring method of V0 was proposed based on the theoretical reason, as well. Clinical investigations of the new V0 to test its efficacy of monitoring are needed.

1. Introduction

Carbon dioxide concentration can be plotted against expired volume (volumetric capnogram, Vcap) during the respiratory cycle. The current trends in monitoring patient safety are leading to the adoption of the capnogram as a standard of care in intensive care units and the importance of Vcap has been recognized (Walsh et al., 2011). One of the earliest descriptions of Vcap and a method to determine "airway" dead space is that of Aitken and Clark-Kennedy (1928). Fowler (1948) in describing the single breath test for nitrogen (SBT-N2) curve sought to use uniform terminology to clarify the "meaning of dead space", and divided this curve into four phases (I, II, III, and IV). Vcap of single breath test (SBT-CO2) also represents four phases resembling SBT-N2 in shape (Bartels et al., 1954). The phase III of Vcap indicates "physiological or alveolar dead space", which means lung units that are ventilating but not contributing to gas-exchange because of no contact with pulmonary capillary blood flow.

"Cardiogenic oscillation" (CarO) is seen in phase III of SBT-N2. CarO has been usually explained by heart beat pulsation transmitted to the lung parenchyma, which represents that resulting changes in the lung volume are sufficient to move small amounts of gas back and forth. However, another explanation for CarO has also been proposed as cyclic changes in pulmonary arterial pressure and flow (Tusman et al., 2009; Suarez-Sipmann et al., 2015). A recent study of Wada et al. (2015, Fig. 1A) has proposed a new graphical analysis of SBT-N2 (named as “the first derivative wave analysis of SBT-N2” or FDWA-N2) by use of the central difference method (Davis and Polonsky, 1972) of digital data, and has revealed that CarO is seen in both III and IV phases of FDWA-N2, and that the phase III is discriminated from the phase IV by difference in amplitudes of CarO, as well. CarO is important to identify the phase III but its genesis is under debate even today.

The lungs are the primary organs of gas exchange. Gas exchange of oxygen (O2) and carbon dioxide (CO2) molecules is a physiological process through which different gas molecules are transferred in opposite directions across a specialized respiratory surface. Classical physiology explains this process in the lung as a result of physical diffusion down a concentration gradient: gas molecules moving from an area of high concentration to low concentration (Wagner, 2005). Classical physiology also explains that both O2 and CO2 are transported throughout the body in erythrocytes through arteries, capillaries and veins. O2 molecules bind to hemoglobin in erythrocytes, and CO2 molecules dissolve in the plasma or combine with water to form bicarbonate ions (HCO3−) with catalyzing action of the carbonic anhydrase (CA) in the erythrocytes. It is well

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known that erythrocytes play the major role of exchanging gas molecules in the lung. (Klocke, 1997) Recent progress in imaging techniques has provided direct observations on oxygenation process of each erythrocyte in the pulmonary parenchyma including arterioles and capillaries, which showed that each erythrocyte performs gas-exchange while moving in the arterioles and capillaries (Tabuchi et al., 2013).

The lung parenchyma is composed of the secondary pulmonary lobules of Miller or the pulmonary lobule of Matsumoto (Miller, 1937; Matsumoto, 1977). The pulmonary lobule is known as a fundamental unit of lung that can reproduce as a miniature the lung structure (Webb, 2006), where pulmonary airways, arteries, veins, lymphatics and the lung interstitium are represented all at its level. That is, the lung parenchyma is composed of aggregated pulmonary lobules, each of which contains arterioles, venules and alveolar capillary beds where erythrocytes perform gas exchange. Therefore, if gas-exchange occurs along arterioles/venules and capillary in the pulmonary lobule, the pulmonary lobule should be described as the functional unit of gas-exchange.

In this paper, the authors defined the pulmonary lobule as the functional unit of gas-exchange, and motion profiles of erythrocytes either as percolation along random-walk in the capillaries or as pulsed-run in the arterioles and venules of the pulmonary lobule. Based on different behaviors of erythrocytes during gas exchanging, we obtained a new mathematical expression for $V_{\text{cap}}$ in the form of FDWA-CO$_2$, which revealed that CaO and the phase III respectively would come from different motion profiles of erythrocytes in the pulmonary parenchyma. By use of the mathematical expression of $V_{\text{cap}}$, we proposed a new theoretical evaluation method of the dead space.
2. Model

2.1. Physiological and anatomical summary as assumptions for modeling

Physiological and anatomical observations of O₂–CO₂ exchange were summarized as follows (Klocke, 1997; Tabuchi et al., 2013, and Matsumoto, 1977), (A1) the erythrocyte produces carbon dioxide molecules from bicarbonate ions in the plasma by a constant rate; (A2) the erythrocyte captures oxygen molecules from the alveolar space by changing the oxygen affinity of hemoglobin molecules (Hb) according to the oxygen equilibrium curve (OEC), which is considered as a statistical curve in number of saturated erythrocytes among a vast number of erythrocytes in the same condition of oxygen pressure; (A3) oxygenation of erythrocytes occurs within 100 msec over a distance of approximately 10 µm in the pulmonary microvasculature, and approximately 50% of oxygenation occurs in pre-capillary arterioles and post-capillary venules; (A4) the alveolar capillary network is defined as a square lattice of sites with the equal length of short cylindrical tubes. However, in this study we adopted a lattice form of network consisting of short cylindrical tubes with the average form of hexagonal wedges. The alveolar capillary network is a large two-dimensional square lattice of sites with the probability of a connected path from the arteriole side to the venule side (percolation) in order to do effective gas exchange. Percolation theory describes trajectories of erythrocytes moving in the capillary precapillary arterioles, the post-capillary venules, and the capillary beds; (A5) the plot of blood flow velocities (Tabuchi et al., 2013) demonstrated the velocity profile of relatively high blood flow velocities in both the arteriole and the venule segments, and of almost zero flow velocities in the alveolar capillary beds, in other words the former is called pulsed-run and the latter is called random-walk; and (A6) a geometrical analysis of precapillary arterioles has revealed that precapillary arterioles (“spider’s pedate arterioles” named by Matsumoto, 1977) are all almost same in the diameter and the length in the secondary pulmonary lobule, and precapillary arterioles and postcapillary venules were not able to be discriminated by their anatomical structures. Weibel (1963) characterized the structural geometry of alveolar capillaries as a two-dimensional stochastic network of short cylindrical tubes with the average form of hexagonal wedges. However, in this study we adopted a lattice form of network consisting of equal length of short cylindrical tubes.

2.2. Random-walk model of erythrocytes in the capillary beds

A random-walk model of gas-exchange at erythrocytes moving in the capillary beds was constructed as follows, (1) as an erythrocyte travels across capillary networks in the alveolar surface, the path traced by the erythrocyte consists of a succession of random steps; (2) the alveolar capillary bed is a large two-dimensional square lattice of sites with the distance \( \theta \) between them, where each edge is independently opened (allowing the erythrocyte to go through it) with probability \( p \) or closed (preventing the erythrocyte from going through it) with probability \( 1 - p \); (3) consider a trajectory as a cluster of connected neighboring sites along random-walk of an erythrocyte.

According to the assumption (A1), each erythrocyte can produce the number of CO₂ molecules \( U_{CO₂} \) proportional to the number of random steps \( s \) of its corresponding trajectory as follows,

\[
J_{CO₂} \propto s
\]  
(E1)

Based on the assumptions (A2) and (A3), each erythrocyte can capture \( O₂ \) molecules \( U_{O₂} \) by changing the oxygen-saturation of Hb (\( \Delta S_{O₂} \)) during more steps than the critical number of steps, \( s_m \),

\[
J_{O₂} \propto \Delta S_{O₂} \cdot \delta_{s_m}
\]  
(E2)

where \( \delta_{s_m} \) is a step function \( \delta_{s_m} = 0, \) if \( s < s_m \); \( \delta_{s_m} = 1, \) if \( s \geq s_m \).

3. Results

3.1. Random-walk and a diffusion equation

A trajectory of random walk from zero to step \( s \) has to obey the master equation as follows (Stauffer and Aharony, 1994),

\[
P_s(s + 1) - P_s(s) = \sum \left[ \sigma_i P_i(s) - \sigma_i P_i(s) \right]
\]  
(E3)

where \( P_s(s) \) is the probability occupied at the site \( i \) by an erythrocyte at the step \( s \), and \( \sigma_i \) is the probability of transition from the site \( i \) to its adjacent site \( j \) with the probability of \( p \) during between steps \( s \) and \( s + 1 \). The alveolar capillary network is defined as a square lattice of distance \( \theta \) between adjacent sites, where erythrocytes move randomly with a probability \( p \) during the time \( t \) and \( t + \epsilon \). Since the alveolar capillary network is a square lattice, the transitional probability \( \sigma_i \) is \( p^4 \).

At the time \( t + \epsilon \), the probability of finding the erythrocyte at the site \( x,y \) is described as follows,

\[
P(x,y,t + \epsilon) = \frac{p^4}{4} \left[ P(x + 0,y,t) + P(x - 0,y,t) + P(x,y + 0,t) + P(x,y - 0,t) \right]
\]  
(E4)

Then, the subtraction \( P(x,y,t + \epsilon) - P(x,y,t) \) is expressed as follows,

\[
P(x,y,t + \epsilon) - P(x,y,t) = \frac{p^4}{4} \left[ P(x + 0,y,t) - 2P(x,y,t) + P(x - 0,y,t) + P(x,y + 0,t) + P(x,y - 0,t) - 2P(x,y,t) \right]
\]  
(E5)

A set of approximations are known as follows,

\[
P(x + 0,y,t) - 2P(x,y,t) + P(x - 0,y,t) \sim \frac{\partial^2 P}{\partial x^2}
\]  
(E6)

\[
P(x,y + 0,t) - 2P(x,y,t) + P(x,y - 0,t) \sim \frac{\partial^2 P}{\partial y^2}
\]  
(E7)

Therefore, the Eq. (E8) is obtained by \( \epsilon \to 0 \) from the Eq. (E5) as follows,

\[
\frac{\partial P}{\partial \epsilon} = \frac{p^4}{4} \left( \frac{\partial^2 P}{\partial x^2} + \frac{\partial^2 P}{\partial y^2} \right)
\]  
(E8)

\[
D_n = \frac{p^4}{4}
\]  
(E9)

The Eq. (E8) has represented a two-dimensional diffusion phenomenon of the diffusion coefficient \( D_n \), which contains a physiological parameter \( p \) and a geometrical parameter \( \theta^2/4 \).

3.2. Percolation (Fig. 2A, B)

It is necessary for every erythrocyte to pass through the capillary beds from the arteriole side to the venule side (percolation) in order to do effective gas exchange. Percolation theory describes trajectories of erythrocytes according to the master Eq. (E3), and can answer the question, “what is the probability that erythrocytes can pass from arterioles to venules under a given opening probability of \( p \)?” Computer simulations (Sedgewick and Wayne, 2016, Fig. 2B) have shown that the probability of a connected path from the arteriole side to the venule side increases sharply from close to 0 to close to 1 within a short span of \( p \). Therefore, there is a critical probability \( p_c \); the percolation probability is 0 or 1 at less and more than it, respectively. That is, when the opening probability \( p \) of capillary branch is more than \( p_c \), every erythrocyte can reach corresponding postcapillary venules. As suggested in the experimental study by Presson and colleagues (Presson et al., 1997) the opening probability \( p \) of capillary branch would be dependent upon the microvascular pressure of alveolar capillaries. If the capillary pressure is less than the critical value, oxygen-saturated erythrocytes cannot reach corresponding venules and cannot contribute to oxygenation of total blood. However, CO₂ shift from blood into alveolar spaces must be independent from percolation process of erythrocytes because erythrocytes...
in the pulmonary parenchyma produce CO₂ from plasma at constant rate. Thus, percolation of erythrocytes across the capillary beds would make some significant difference between O₂-uptake and CO₂-elimination in the pulmonary parenchyma.

3.3. Two types of motion profiles

3.3.1. Proportion of motion profiles in the transit time

Erythrocytes are running in the pulmonary parenchyma which consists of the pulmonary secondary lobule of Miller. Based on the assumption (A6) the pulmonary secondary lobule contains intralobular arterioles, alveolar capillary beds and intralobular venules, and according to the assumption (A5) two types of motion (pulsated-run in the arterioles/venules and random-walk in the capillary beds) would be seen in the pulmonary parenchyma. No precise description about the proportion of number of erythrocytes in either pulsated-run or random-walk has been reported until today.

Transit time (τ) for each erythrocyte passing through the pulmonary parenchyma is composed of both the time in pulsated-run (τₚᵤₐₙ) and that in random-walk (τᵣₑₙ); i.e., τ = τₚᵤₐₙ + τᵣₑₙ. When the ratio of τᵣₑₙ and τ is described by μ, each transit time is defined as follows,

\[ \tau_{\text{pul}} = (1 - \mu) \tau \]  
\[ \tau_{\text{rw}} = \mu \tau \]  

3.3.2. Gas-exchange in an erythrocyte

Gas exchange is performed by each erythrocyte during both motion profiles of pulsated-run and of random-walk. If the transit time is proportional to the number of steps, each erythrocyte can produce the number of CO₂ molecules (\( J_{\text{CO}_2} \)) that is proportional to its transit time (τ) in the pulmonary lobule as follows,

\[ J_{\text{CO}_2} \propto \tau = (\tau_{\text{pul}} + \tau_{\text{rw}}) = \tau(1 - \mu) + \tau(\mu) \]  

Each erythrocyte can capture O₂ molecules by changing the oxygen-saturation of Hb molecules themselves (\( \Delta S_{\text{O}_2} \)) during the passing across the pulmonary lobule according to \( J_{\text{O}_2} \). Since the time of pulsated-run (\( \tau_{\text{pul}} \)) would usually be longer than the sufficient time (\( \tau_{\text{m}} \)) necessary for complete saturation of Hb, from (E2) to the equation for capturing oxygen molecules by an erythrocyte was defined as follows,

\[ J_{\text{O}_2} \propto \Delta S_{O_2}\Delta \tau_{\text{m}} = \Delta S_{O_2}\left(\delta_{\text{pul}} + \delta_{\text{rw}} + \delta_{\text{m}}\right)/2 = \Delta S_{O_2}(1 + f_{\text{rw}})/2 \ldots \]  

where \( \delta_{\text{pul}} \) or \( \delta_{\text{rw}} \) is the step function (\( \delta_{\text{pul}} = 0 \) if \( \tau < \tau_{\text{m}} \), \( \delta_{\text{rw}} = 1 \) if \( \tau \geq \tau_{\text{m}} \)), respectively, and \( f_{\text{rw}} \) is the fractional ratio of erythrocytes passed longer than the critical time (i.e., \( f_{\text{rw}} = \sum \delta_{\text{pul}}/N_e \), where \( N_e \) is the total number of erythrocytes passed through capillary beds).

3.3.3. Gas-exchange equations and Vcap

According to the classical physiology of pulmonary gas-exchange equations, a set of equations for gas-exchange in the pulmonary lobule of l is expressed as follows (Wagner, 2005),

\[ P'_{\text{A}CO_2} \cdot V'_{\text{A}O_2} \cdot (C_{\text{A}CO_2} - C_{\text{A}O_2}) \cdot \delta' \]  
\[ P'_{\text{A}O_2} \cdot V'_{\text{A}CO_2} \cdot (C_{\text{A}O_2} - C_{\text{A}CO_2}) \cdot \delta' \]  

where \( P'_{\text{A}CO_2} \) and \( P'_{\text{A}O_2} \) are the alveolar carbon dioxide pressure and the alveolar oxygen pressure in the pulmonary lobule l, respectively; \( V'_{\text{A}} \) is the alveolar ventilation volume of the pulmonary lobule l; \( C_{\text{A}CO_2} \), \( C_{\text{A}O_2} \), \( C_{\text{A}CO_2} \), and \( C_{\text{A}O_2} \) are contents of carbon dioxide and oxygen gases in the pulmonary venous and arterial blood, respectively; and \( \delta' \) is the blood flow including a number of erythrocytes \( n'_{e} \) into the pulmonary secondary lobule of l. When the average of transit times among erythrocytes in the pulmonary lobule l is \( \tau \) (= \( \tau_{\text{pul}} \) + \( \tau_{\text{rw}} \)), from Eqs. (E14) and (E15) a new set of equations for the lobular gas-exchange is obtained as follows,

\[ P'_{\text{A}CO_2} \cdot V'_{\text{A}O_2} \cdot (C_{\text{A}CO_2} - C_{\text{A}O_2}) \cdot \delta' \cdot (\tau_{\text{pul}} + \tau_{\text{rw}}) = n'_{e} \tau_{\text{pul}} + n'_{e} \tau_{\text{rw}} \]  
\[ = N'_{e}(1 - \mu') + N'_{e} \mu' \]  

(\[ E16 \])

\[ P'_{\text{A}O_2} \cdot V'_{\text{A}CO_2} \cdot (C_{\text{A}O_2} - C_{\text{A}CO_2}) \cdot \delta' \cdot \Delta S_{\text{O}_2} \]  
\[ = N'_{e} \mu' \cdot S_{\text{O}_2} \]  

(\[ E17 \])
where suffix l indicates that every parameter is observed in the lobule l, and Nl is total number of erythrocytes in the lobule l. When N number of lobules are contributing to a volume of ventilate Vl, the equation of gas-exchange (PACO2 and PAO2) for the lung can be obtained by summation of (E16) or (E17) through the whole lung as follows.

\[
P_{\text{ACO}_2} \cdot V_A = \sum_{l=1}^{N} P_{\text{ACO}_2} \cdot V_l \propto \sum_{l=1}^{N} \left\{ N_l \left(1 - \mu \right) + N_l \mu \right\}
\]

\[
= N_e (1 - \mu) + N_e \mu \tag{E18}
\]

\[
P_{\text{AO}_2} \cdot V_A = \sum_{l=1}^{N} P_{\text{AO}_2} \cdot V_l \propto \sum_{l=1}^{N} \left\{ N_l \left(1 - \mu \right) \Delta \Delta N_l + N_l \mu \Delta \Delta N_l \right\}
\]

\[
= \Delta \Delta N_e (1 - \mu) N_e + \Delta \Delta N_e \mu N_e \tag{E19}
\]

where Ne is the total number of erythrocytes, and \( \Delta \Delta N_l \), \( \Delta N_l \), or \( \mu \) is the mean value of \( \Delta \Delta N_l \), \( \Delta N_l \), or \( \mu \) respectively among pulmonary lobules contributing to the exhaled volume of Vl. According to the ergodic rule of statistical physics, it is assumed that the time proportion between motion profiles (\( \mu \)) would become equal to a topographical proportion between the arterioles/venules and the capillary beds. Therefore, among the total number of Ne of erythrocytes contributing to the exhaled volume of Vl, the number of erythrocytes in pulsed run was defined by Ne(1 - \( \mu \)), and those in random walk was defined by Ne\( \mu \).

By partial differentiation the Eq. (E18) twice regarding with Vl, we obtained the expression of Vcap as follows,

\[
\frac{\partial P_{\text{ACO}_2}}{\partial V_A} \propto (1 - \mu) \frac{\partial^2 N_e}{\partial t^2} + (\mu) \frac{\partial N_e}{\partial V_A} \tag{E20}
\]

Concerning the type of motion profiles for pulsed run or random walk, two motion equations were introduced as follows,

\[
c^2 \frac{\partial^2 N_e}{\partial t^2} = \frac{\partial N_e}{\partial t} \tag{E21}
\]

\[
D_w \frac{\partial^2 N_e}{\partial t^2} = \frac{\partial N_e}{\partial t} \tag{E22}
\]

where c or Dw is respectively a velocity of oscillation-wave or a diffusion coefficient along the axis of VA. Therefore, Vcap was defined by the motion equation as follows,

\[
\frac{\partial P_{\text{ACO}_2}}{\partial V_A} \propto (1 - \mu) \frac{c^2}{\partial t^2} \frac{\partial^2 N_e}{\partial t^2} + \frac{\partial N_e}{\partial D_w} \tag{E23}
\]

3.3.4. First derivative analysis of Vcap

Pulmonary blood flow is produced by both cardiac contraction and elastic pulmonary arterial wall. Erythrocytes run through pulmonary parenchyma along with pulmonary blood flow. Right heart catherization has revealed that pulmonary arterial blood flow is composed of the oscillated part and the constant part. Thus, the total number of erythrocytes (Ne) in the pulmonary blood flow would be expressed as follows,

\[
N_e(t) = \int_0^t A_g(\mu) du + Bt \tag{E24}
\]

where \( A_g(\mu) \) and B are respectively the oscillated part and the constant part. Thus, the equation for Vcap was expressed as follows,

\[
\frac{\partial P_{\text{ACO}_2}}{\partial V_A} \propto \frac{(1 - \mu)}{c^2} \frac{\partial^2 N_e}{\partial t^2} + \frac{\partial N_e}{\partial D_w} \tag{E25}
\]

(E25) has showed that Vcap consists of the oscillating part and the constant part; the first clause represents the forced oscillating system of the damper \( (1 - \mu)/c^2 \) driven by the periodic force of \( A_g(\mu) \) (‘cardiogenic oscillation’), and the second clause represents that the gradient of phase III comes from random-walk of erythrocytes in the capillary beds.

3.3.5. Transfer factor of CO diffusion (Tco) and slope of phase III

The rate of carbon monoxide (CO) uptake from the lungs is the product of alveolar partial pressure of CO in excess of any back pressure in the blood (driving pressure) and a rate constant. The single breath diffusing capacity method is performed by having the subject blow out as much air as possible, leaving only the residual lung volume. The subject then rapidly and completely inhales a gas mixture containing a tracer gas such as helium, reaching the total lung capacity as much as possible. The tracer gas is held in the lung for about 10 seconds during which time the CO continuously moves from pulmonary parenchyma into the blood. The CO uptake from the lung (DlCO) is measured as a change in concentration of CO per a change in pressure. Since molecules of CO have very high affinity to hemoglobin molecules (Hb), Hb in each erythrocyte in the alveolar capillary beds would be rapidly and completely saturated (\( \Delta \Delta \text{CO} = 1.0 \)) during the time of \( \Delta t \). Thus, \( \text{Tm} \) and \( \Delta \Delta \text{CO} \) respectively must be 1.0 in (E19). The equation for CO uptake in the single breath diffusion capacity method is described by the same equation as (E20) as follows,

\[
\frac{\partial P_{\text{ACO}_2}}{\partial V_A} \propto \frac{(1 - \mu)}{c^2} \frac{\partial^2 N_e}{\partial t^2} + \frac{\mu}{D_w} A_g(t) + \left( \frac{\mu}{D_w} B \right) \tag{E26}
\]

Then, the transfer factor for CO (Tco = DlCO/VA) would be proportional to the slope of phase III of Vcap as follows,

\[
T_{\text{CO}} = \int_0^{10} \frac{\partial P_{\text{ACO}_2}}{\partial V_A} \; dt/\int_0^{10} \left[ \frac{(1 - \mu)}{c^2} \frac{\partial^2 N_e}{\partial t^2} + \frac{\mu}{D_w} A_g(t) \right] dt
\]

\[
+ \int_0^{10} \left( \frac{\mu}{D_w} B \right) \; dt \tag{E27}
\]

3.3.6. Dead space

The excreted volume of carbon dioxide (EACO2) into the pulmonary parenchyma during a tidal breathing of volume VT or a breath time of T is defined by use of (E25) as follows,

\[
E_{\text{ACO}_2} = \int_0^{V_T} \frac{\partial P_{\text{ACO}_2}}{\partial V_A} \; dV \propto T \left[ \left( \frac{(1 - \mu)}{c^2} \frac{\partial^2 N_e}{\partial t^2} + \frac{\mu}{D_w} A_g(t) + \frac{\mu}{D_w} B \right) \right] dt
\]

\[
= \left( \frac{\mu}{D_w} B \right) T \tag{E28}
\]

Since the flow rate of carbon dioxide (EACO2/T) is proportional to the slope of phase III, EACO2 during a breath is evaluable as the area of trapezoid 1-2-3-4 (see Fig. 3). The actual excreted volume of CO2 is measurable as the area under curve of Vcap (AUVcap). Therefore, the dead space in this case must be described by \( (1 - \text{AUV}_{\text{cap}}/E_{\text{ACO}_2} )/VT \).

4. Discussion

4.1. Geometrical properties of pulmonary capillary network and percolation

Although Weibel (1963) characterized the structural geometry of alveolar capillaries as a two-dimensional stochastic network of short cylindrical tubes with the average form of hexagonal wedges with two adjacent segments, in this study we adopted a lattice form of network consisting of equal length of short cylindrical tubes. Geometrical difference in the capillary network is well known to produce the difference of the critical probability in the percolation phenomenon (\( p_c \) in the section...
3.2, \( p_c = 0.6962 \) for honeycomb and \( p_c = 0.592746 \) for square). (Broadbent and Hammersley, 2008) However, it is noted that motion profiles of erythrocytes are described by the diffusion equation of a corresponding appropriate diffusion coefficient even in different forms of network like the equation of (E8). Anyway, it is important to recognize that pulmonary perfusion is achieved by the rule of all-or-none based on percolation theory.

4.2. CarO and phase III in FDWA-CO₂

4.2.1. The first derivative wave analysis (FDWA)

By constructing the ratio of a change in N₂ concentration of exhaled gas with regard to the change of exhaled lung volume (20ml), Wada and colleagues (Wada et al., 2015) introduced a new graphical analysis of SBT-N₂ curve (FDWA-N₂, Fig. 1A) where the phase III was composed of cardiogenic oscillations (CarO) and constant (which indicates the slope of phase III in SBT-N₂). It was able to distinguish phase IV from phase III using the difference in amplitude of CarO in FDWA-N₂. In this study we applied FDWA to the volumetric capnogram of single breath test (SBT-CO₂). CarO have been neglected in usual SBT-CO₂ because of being less than SBT-N₂. FDWA-CO₂ showed however clear oscillations in the latter part of phase III as shown in Fig. 1B, which is composed of noisy changes of small amplitude in the early part followed by large amplitudes of waves. CarO of FDWA-CO₂ would be explained as a resonance in forced damping oscillations based on the mathematical model of (E25).

The velocity \( c \) representing the cardiogenic waves in FDWA-CO₂ is evaluable by product of \( \lambda \) (the wave length) and \( \nu \) (the heart rate). Since the parameter \( c \) represents pulsed-run in arterioles/venules in the pulmonary parenchyma, the parameter \( c \) would become useful for diagnosing pulmonary vascular diseases. For confirming this hypothesis,
clinical studies are needed.

4.2.2. Slope of phase III

The origin of phase III slope has been attributed to 1) continuous excretion of \( \text{N}_2 \) into the alveoli becoming smaller by the end of expiration, and/or 2) late emptying of alveoli with low ventilation-perfusion ratio containing relatively higher \( \text{N}_2 \) concentration. The standard explanation of phase III slope is based on the concept that gravity causes unequally ventilated lung through the deformation of lung tissue (Slink effect), and uneven perfusion through combination of the Slinky effect and the zone model of pulmonary perfusion. However, when SBT-N\(_2\) were performed repeatedly in parabolic flights and in spaceflights, all of the signatures of ventilator heterogeneity persisted. The terminal rise in \( \text{N}_2 \) concentration in SBT-N\(_2\) (phase IV) was greatly reduced in microgravity, but the persistence of a phase IV is evidence that both ventilation and perfusion exhibit persisting heterogeneity in microgravity indicating important other mechanisms (Prisk, 2014).

Our mathematical model in this study can provide another gravity independent mechanism for phase III: since the number of erythrocytes \( \mu / \text{B} \) is a constant flux of erythrocytes flowing into the pulmonary capillary beds, the mathematical expression (E25) has revealed the slope of phase III (\( \mu / \text{B}_{\text{na}} \)) in Vcap represents the gradient in number of erythrocytes between sides of arterioles and venules in the pulmonary capillary beds. As reported experimental study of Presson et al. (1997), the gradient of erythrocytes in number would relate to microvascular pressure in the capillary beds. Thus, since pulmonary microvascular pressure change in the microgravity environment would be most important to understand the phase III, it is necessary to investigate what physiological and geometrical changes are seen in pulmonary vascular system under the microgravity environment.

\( T_{\text{CO}} \) of (E27) suggested a close relationship between the phase III slope and \( T_{\text{CO2}} \), both of which represents the gradient in number of erythrocytes between the pulmonary arterioles and venules. Thus, the validity of our mathematical model would be evaluated by a close relationship between \( T_{\text{CO}} \) and the phase III slope of Vcap among various conditions including parenchymal lung diseases.

4.3. Dead space

The dead space (V\(_D\)) refers to lung units that are ventilated but do not contribute to gas exchange because the expired gas from these units has no contact with pulmonary capillary blood flow. In 1891, Bohr proposed an equation to calculate dead space normalized tidal volume (V\(_T\)):

\[
V_D / V_T = \left( P_{\text{ACO}_2} - P_{\text{ECO}_2} \right) / P_{\text{ACO}_2}
\]

\( P_{\text{ACO}_2} \) is alveolar \( P_{\text{CO}_2} \) and \( P_{\text{ECO}_2} \) is mixed expired \( P_{\text{CO}_2} \). However, \( P_{\text{ACO}_2} \) is not readily available. In 1938, Enghoff proposed an adaptation of Bohr’s equation in which \( P_{\text{CO}_2} \) is used instead of \( P_{\text{ACO}_2} \). Substitution of \( P_{\text{ACO}_2} \) for \( P_{\text{ACO}_2} \) produces some confusion in the interpretation of the mechanism of dead space production. As the discussion by Verschueren et al. (2016), Enghoff’s substitution has been known as valid only in an ideal lung of perfect ventilation-perfusion matching for all units, but is never applicable to the case of pulmonary diseases.

By use of an equal area method proposed by Tang et al. (2006), we have also described difference among Bohr, Enghoff, and our approaches to the dead space in Fig. 4, in which the line discriminating between the dead space (V\(_D\)) and the alveolar gas-exchange space is created so that area A equals to area B. Our model would provide the smallest V\(_D\) among three models as the real dead space because that \( \text{CO}_2 \) molecules may distribute diffusely in the pulmonary parenchyma including bronchioles. At the bedside Vcap will allow us more precise measurement of real dead space on a breath-by-breath basis. Therefore, we will propose that further clinical research on dead space of Vcap measured by our model is necessary for guiding effective therapy in the emergency department, operating room and intensive care unit.

5. Conclusion

On the basis of motion profiles of erythrocytes in the pulmonary parenchyma, a new mathematical expression for the volumetric capnography (Vcap) was proposed in this paper. The mathematical expression of Vcap provided theoretical explanations for genesis of the phase III slope and of cardiogenic oscillations (CarO), respectively. Validity of our mathematical model will be assessed by the close relationship between the slope of phase III of Vcap and the transfer factor of CO. In addition, the velocity of CarO in the first derivative wave analysis (FDWA) of Vcap was suggested as a physiological indicator for estimating elastic properties of pulmonary arterioles. We have also proposed a more precise measurement of dead space based on the mathematical model. For guiding more appropriate therapy of patients in the emergency department, operating room and intensive care unit, clinical researches by use of our measurement of dead space are needed.

Declarations

Author contribution statement

Kyongyob Min: Analyzed and interpreted the data; Wrote the paper. Shinichi Wada: Conceived and designed the experiments; Performed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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