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Multicompartment Model of Lung Dynamics*

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A mathematical model was developed to simulate the function of the lungs. The lungs are represented by 24 compartments each corresponding to a generation of the Weibel model A. In the model it is assumed that gases are transported in the lungs by convection and diffusion from one compartment to the other. Furthermore, the clearance of gases from the lungs by the blood perfusion is taken into account. The driving force of the inhalation and exhalation processes is the filling and emptying of the alveolar volume which follows a sinusoidal pattern. Mathematically the model is represented by two sets (one for inhalation, the other for exhalation) of 24 first-order coupled ordinary differential equations which were numerically integrated by means of a computer. The model predicts quite well the buildup of gases in the lungs and the washout of gases from the lungs.

INTRODUCTION

Radioactive (*1*) and nonradioactive (*2–4*) gases are often used to study the ventilation and perfusion of human lungs. The lungs are a complex organ and the interpretation of clinical data requires a knowledge of the transport of gases within the organ. Since it is difficult to carry out measurements of the gas transport inside of the lungs *in vivo*, one has to rely on mathematical models. The models can then be verified by comparing the results of the modeling to some experimentally observed quantities or processes such as, for example, washout curves.

This paper presents a multicompartment lung model consisting of 24 interconnected compartments, each corresponding to a generation of the Weibel model (*5*). The model assumes that gas is transported through the lungs by convection and diffusion processes. The advantage of compartmentalization of the lungs is that that "local effects" (for example, diffusion, which can only be modeled over some generations) can easily be incorporated into the model. Another advantage of the model is that the initial conditions can easily be defined which is not always the case with partial differential equations of the second order. This paper presents the formulation of the model, and the calculation of uptake and washout processes and the concentration profiles of gas during the initial inhalation–exhalation cycles.

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Theoretical Approach

Morphometric Lung Model

Weibel's model A (*5*) was used in this study. This model assumes that the airways multiply by regular dichotomy (or branching into two) and that all elements (branches) in a given generation have identical dimensions. The airway structures of Weibel's model branch over 24 generations with the trachea representing the 0th generation. The lung is divided into two zones: the conductive zone comprising generations 0 to 16 and the transitory–respiratory zone covering generations 17 to 23. The inner surfaces of the airways in generations 17 to 19 are partially covered with alveoli and fully covered with alveoli in generations 20 to 23. A mouth compartment has been added to Weibel's model and it is represented by a tube with a volume of 20 ml. Thus, in all calculations presented here, mouth breathing has been assumed.

Mathematical Model

Scherer *et al.* (*6*) and Paiva and Paiva-Veretennicoff (*7*) mathematically described the transport of gases in human lungs by a partial differential equation of second order in distance and first order in time. In this work we replaced the partial differential equation (*6*, *7*) by two systems (one system describing inhalation, the other exhalation) of 25 first-order coupled ordinary differential equations.

The assumptions made in this work were similar to the ones made by Scherer *et al.* (*6*) and Paiva and Paiva-Veretennicoff (*7*). It is assumed that

(a) the axes of the airways are in the same plane (i.e., the flow and diffusion are in one dimension only);

(b) the concentration of gas in question is equal over the whole volume of the generation, including the alveolar volume;

(c) the volume of the bifurcation is negligible (*7*); and (d) the wall between the airways of a particular generation can be removed (*7*).

Each generation of the Weibel model is represented by one compartment in our model, with the volume corresponding to the total volume of the airways (Fig. 1). The alveolar volume is superimposed on the volume of the airways for generations 17 to 23. The expansion and contraction of the alveolar volume was assumed to be the driving mechanism for the inflow and outflow of gases (*6*). The dimensions of the airways were assumed constant during the breathing which is a good approximation since the variation in the airways was found to vary only by about 7% from the average values (for the tidal volume of 1000 ml) (*8*). Furthermore, it is assumed that diffusion between compartments is negligible in the first 12 compartments (*7*) and a sinusoidal breathing pattern (*6*) (see below) is used.

The inhaled gas will diffuse across the alveolar membrane and dissolve in the blood circulating through the lungs. The dissolved gas will be cleared from the lungs as a result of the blood perfusion (*9*). Of the two processes the diffusion

of the gas across the membrane can be neglected since it is not a limiting process (*9*). The rate of dissolved gas removed from the lungs due to the blood perfusion was estimated to be 2.1 liters min^{-1} (*10*) corresponding to a half-life of 20 sec. In our model it is assumed that the removal of the dissolved gas by the blood perfusion occurs only in the respiratory region of the lung (generations 17 to 23) which roughly represents 98% of the total airway surface (*5*). Furthermore, the transfer of the dissolved gas from the circulating blood into the lungs (*11*) was also taken into account.

Inhalation

Taking into account the above assumptions the system of differential equations describing the inhalation process can be written (see also Fig. 1). For the mouth compartment we have

$$dA_m(t)/dt = (C_{out} - A_m(t)/V_m)Q_m(t)$$

where $A_m(t)$ represents the amount of gas in question in the mouth (as moles or number of gas molecules), $Q_m(t)$ is the total flow rate of all gas into the mouth (see below), V_m is the volume of the mouth, and C_{out} is the concentration of the gas of interest outside the mouth. If we are interested in washout studies C_{out} is set to zero. From generation 0 (trachea) to generation 12 where diffusion can be neglected, the gas transport is described by

$$dA_j(t)/dt = -A_j(t)Q_j(t)/V_j(t) + A_k(t)Q_k(t)/V_k(t) \qquad \text{for } j = 0, 1, 2, \ldots, 12$$

where A_j, Q_j, and V_j, represent the amount of gas, gas flow rate, and the volume of the jth generation, and $k = j - 1$. For the mouth compartment $m = j = -1$.

Diffusion occurs in generations 13 to 22 and the equations for these generations are

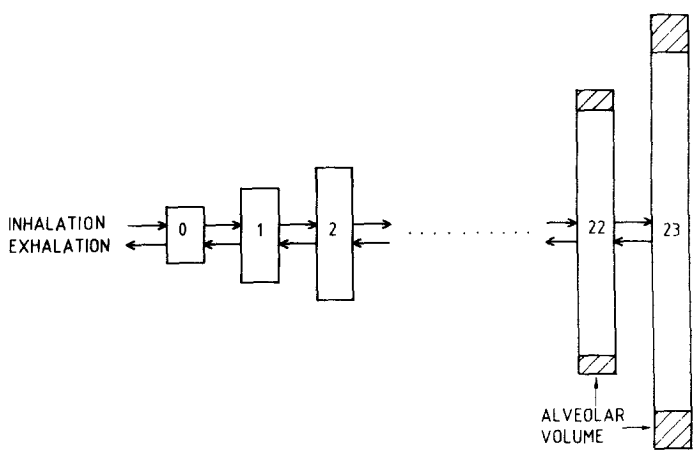

FIG. 1. Schematic representation of the multicompartment lung model. Shaded areas represent the alveolar volume.

$$dA_j(t)/dt = -A_j(t)Q_j(t)/V_j(t) + A_k(t)Q_k(t)/V_k(t) - D[A_j(t)/V_j(t) - A_i(t)/V_i(t)]S_j/L_{j,i} - D[A_j(t)/V_j(t) - A_k(t)/V_k(t)]S_k/L_{k,j} - \begin{cases} 0 \text{ when } j = 13, \ldots, 16 \\ r(\lambda A_j(t) - A_b) \text{ when } j = 17, \ldots, 22 \end{cases} \quad \text{for } j = 13, 14, \ldots, 22$$

where D is the diffusion constant of the gas in question and S_k is the average cross section at the bifurcation between the two generations (*6*) and $i = j + 1$. The gradient is assumed to occur over the distance from the middle of a generation airway to the middle of the following ($L_{j,i}$) or preceding ($L_{j,k}$) one. These distances are fairly short (~0.5 mm) in the generations where the diffusion occurs. For the last compartment we have

$$dA_{23}(t)/dt = A_{22}(t)Q_{22}(t)/V_{22}(t) - D[A_{23}(t)/V_{23}(t) - A_{22}(t)/V_{22}(t)]S_{22}/L_{22,23} - r(\lambda A_{23}(t) - A_b).$$

The dissolution of inert gas in the blood and its removal from the lungs was taken into account by subtracting a term $\lambda r A_j(t)$ from the right-hand side of the equations for the respiratory region (generations 17 to 23). The parameter λ represents the Ostwald solubility coefficient and r is the rate of removal (*10*). The term rA_b, where A_b is the amount of gas dissolved in blood, represents the rate of transport of the dissolved gas by the circulating blood into the lungs (*9*).

Exhalation

Equations for the exhalation can be derived similarly. For the mouth compartment we have

$$dA_m(t)/dt = -A_m(t)Q_m(t)/V_m + A_0(t)Q_0(t)/V_0$$

and for generations 0 to 12 the equations are (no diffusion)

$$dA_j(t)/dt = -A_j(t)Q_j(t)/V_j(t) + A_i(t)Q_i(t)/V_i(t) \qquad \text{for } j = 0, 1, 2, \ldots, 12.$$

For the generations with diffusion the equations have the form

$$dA_j(t)/dt = -A_j(t)Q_j(t)/V_j(t) + A_i(t)Q_i(t)/V_i(t) - D[A_j(t)/V_j(t) - A_i(t)/V_i(t)]S_j/L_{j,i} - D[A_j(t)/V_j(t) - A_k(t)/V_k(t)]S_k/L_{k,j} - \begin{cases} 0 \text{ if } j = 13, \ldots, 16 \\ r(\lambda A_j(t) - A_b) \text{ when } j = 17, \ldots, 22 \end{cases} \quad \text{for } j = 13, 14, \ldots, 22.$$

For the last compartment (generation) we have

$$dA_{23}(t)/dt = -A_{23}(t)Q_{23}(t)/V_{23}(t) - D[A_{23}(t)/V_{23}(t) - A_{22}(t)/V_{22}(t)]S_{22}/L_{22,23} - r(\lambda A_{23}(t) - A_b).$$

Flow Rate Function

We assumed a sinusoidal breathing pattern with the flow rate at the mouth described by the function (*6*)

$$Q_m(t) = \dot{V}_T(t) = Q_0 \sin(2\pi t/p)$$

where t represents time and p is the breathing period. (Most calculations were carried out by assuming $p = 4$ sec (2 sec for inhalation and 2 sec for exhalation).) Q_0 is defined by the condition

$$\int_0^{p/2} Q_m(t)\, dt = \mathrm{TV}$$

where TV represents the tidal volume. In the alveolated region the local flow rate is given by (*6*)

$$Q_j(t) = Q_m(t)\left[1 - \frac{1}{N_{AT}} \sum_{l=17}^{j} n_{A,j}\right]$$

where N_{AT} is the total number of alveoli (3×10^8) (*5*), and $n_{A,j}$ is the number of alveoli in the jth generation. The equation assumes that the alveoli expand uniformly around the airways (*6*). The total volume of the jth compartment (generation) also varies with time (*6*).

$$\begin{aligned} V_j(t) &= V_{\mathrm{airway},j} + V_{\mathrm{alveoli},j}(t) \\ &= V_{\mathrm{airway},j} + n_{A,j}/N_{AT}[V_T(t) + V^0_{AT}] \end{aligned}$$

where $V_T(t)$ is the tidal volume and V^0_{AT} is the total alveolar volume at the beginning of the inspiration (approximately 1000 ml, assuming normal breathing). The values for $V_{\mathrm{airway},j}$ were taken from Ref. (*5*).

Results

The system of differential equations describing the lung dynamics was solved on a CYBER 170/720 (Model 175) computer system using the FORSIM package for numerical integration of coupled differential equation systems (*12*). For these calculations a Gear's stiff (variable step) integration algorithm with space Jacobian matrix was found to be the fastest. For the inhalation/exhalation sequence the computer first solves the inhalation differential equations (the first 2 sec) and then continues on to solve the exhalation differential equations (for another 2 sec) and then repeats the cycle.

Buildup of Radioactive Gas in Lungs

Figure 2 shows the buildup of ^{133}Xe and T_2 both with a concentration of 1 nmole/ml. A tidal volume of 500 ml (assuming breathing at rest) and a breathing period of 4 sec corresponding to a breathing rate of 15 breaths per minute were assumed in the calculations. The diffusion constants for ^{133}Xe and T_2 were

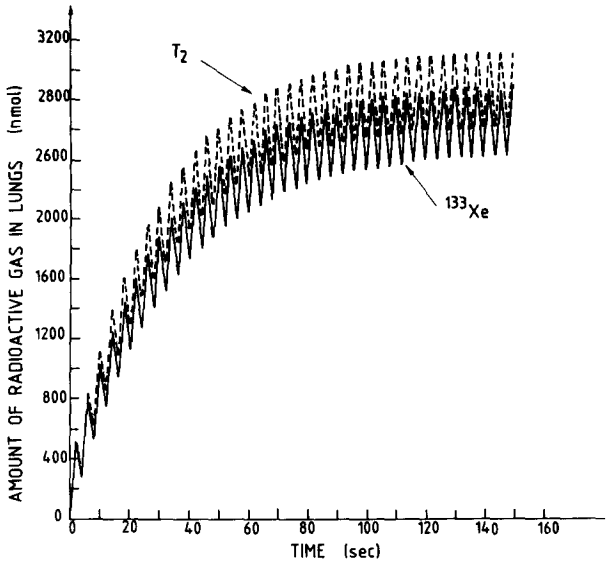

FIG. 2. Buildup of ^{133}Xe (solid line) and T_2 (broken line) in lungs. The values for the tidal volume and breathing frequency of 500 ml and 15 times per min were used.

estimated using the relationship

$$D_u = D_k \left(\frac{M_k}{M_u}\right)^{1/2}$$

where D_u and D_k are the unknown and known diffusion constants, respectively, and M_u and M_k are the unknown and known molecular weights of gases, respectively. The diffusion constant for N_2 of 0.225 $cm^2\ sec^{-1}$ (*7*) was used for D_k. The values of the solubility coefficients for Xe and T_2 of 0.13 (*13*) and 0.016 (*14*) were used in calculations. ^{133}Xe and T_2 have half-lives of 5.31 days (*10*) and 12.6 years (*15*), respectively, which are very long compared to the 2.5 min over which the uptake was calculated. Thus, the radioactive decay of the gases was neglected. Figure 2 shows that T_2 gas will build up to a higher equilibrium value, which is due to the higher diffusion constant and due to the smaller solubility in blood. The half-life for the buildup of ^{133}Xe is about 20 sec which favorably agrees with the value of 30 ± 11 sec reported by Turkin and Moskalev (*16*). Figure 3 shows the relative concentration profiles during the first inhalation/exhalation cycle. The concentration of gas in the higher generations (17 to 23) only gradually increases due to the larger volumes of these generations although the amount of gas in these generations is the highest (Fig. 4). Terminal alveoli (generation 23) represent some 50% of the area available for gas–blood exchange in the lungs (*5*). Therefore it is of interest to see how fast the radioactive gas inhaled reaches the terminal alveoli. Figure 5 shows that

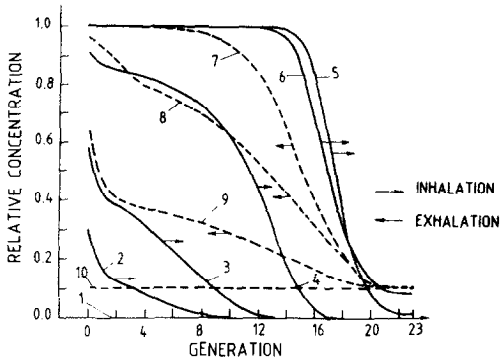

FIG. 3. Relative concentration profiles during the first inhalation (solid line) and exhalation (broken line) for the ^{133}Xe buildup in lungs. The arrows to the right indicate the movement of the front during the inhalation. The arrows pointing to the left indicate the movement of the front during the exhalation. The number indicates the time at which the profile was calculated: (1) 0.0 sec, (2) 0.3 sec, (3) 0.4 sec, (4) 0.6 sec, (5) 1.2 sec, (6) 2.0 sec, (7) 2.3 sec, (8) 2.5 sec, (9) 2.7 sec, and (10) 4.0 sec.

radioactive gas starts entering the terminal alveoli 1 sec after the start of inhalation and reaches its peak at about 2.5 sec after the beginning of the inhalation.

Single breath experiments done with ^{133}Xe on normal subjects indicate that the buildup of xenon in the lower part of the lungs occurs between 2 to 3 sec after the beginning of the inhalation (*17*) which is in good agreement with our calculations.

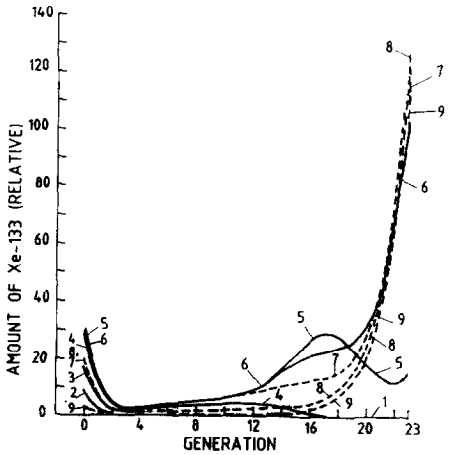

FIG. 4. Distribution of the amount of gas during the first inhalation (solid line)/exhalation (broken line) for ^{133}Xe buildup in lungs. The number indicates at which time the profile was calculated: (1) 0.0 sec, (2) 0.3 sec, (3) 0.4 sec, (4) 0.6 sec, (5) 1.2 sec, (6) 2.0 sec, (7) 2.3 sec, (8) 2.7 sec, and (9) 4.0 sec.

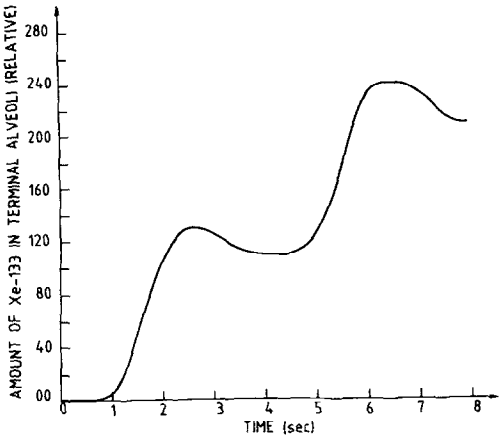

FIG. 5. Buildup of ^{133}Xe in the last (terminal alveoli) generation over two inhalation/exhalation cycles.

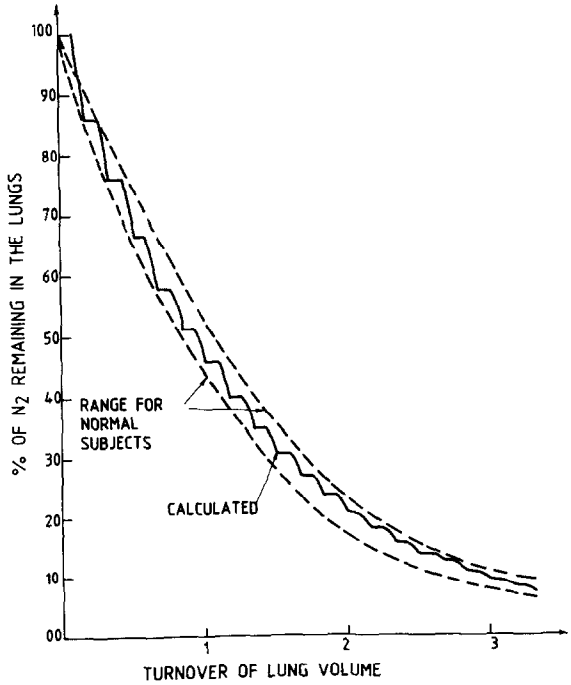

FIG. 6. Comparison between the calculated N_2 washout curve (solid line) and the range (dashed lines) for the experimental washout curves obtained for the normal subjects.

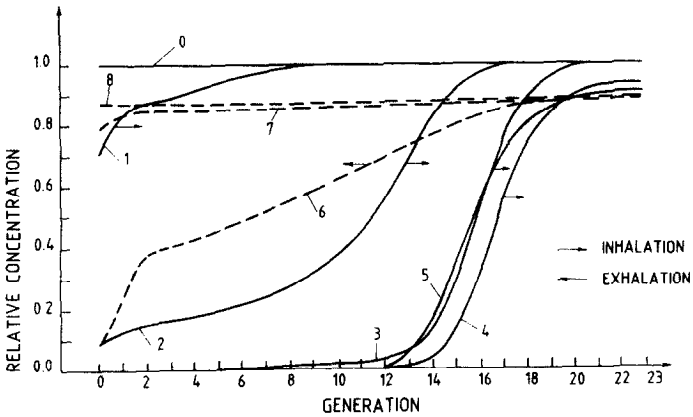

FIG. 7. The relative concentration gas profiles during the inhalation (solid line)/exhalation (broken line) for the N_2 washout. The arrows pointing to the right indicate the movement of the front during the inhalation, and the arrows pointing to the left indicate the movement of the front during the exhalation. The numbers indicate the profiles at times: (0) 0.0 sec, (1) 0.3 sec, (2) 0.6 sec, (3) 0.9 sec, (4) 1.6 sec, (5) 2.0 sec, (6) 2.5 sec, (7) 2.9 sec, and (8) 4.0 sec.

Washout of Nitrogen from Lungs

Nitrogen decay curves are valuable in the diagnosis of the lung diseases (*2–4*). Figure 6 shows the calculated nitrogen decay curve using our model. Nitrogen dissolves in blood only to a small extent (solubility coefficient 0.015 (*14*)) and therefore the transport of dissolved nitrogen from blood into the airways of the lungs was neglected. The calculated curve was compared with the range of the nitrogen decay curves obtained for normal subjects (*4*). As can be seen in Fig. 6 the calculated curve lies within the range for normal subjects. From Fig. 6 one can estimate the half-life of the nitrogen washout which is about 20 sec. Similar values (21.7 ± 12.4 sec) were reported for the washout of ^{133}Xe (*11*). Figure 7 shows the concentration profiles during the first inhalation and exhalation (after the equilibration with N_2 was achieved). As in the case of inhalation the high concentration changes occur in the first 15 generations and the last generations, 17 to 23, empty very slowly. Again this is due to the very large volume of the last generations.

CONCLUSION

The model described above gives a good agreement with the measured functions of the lungs (half-lives for the buildup and washout of the inert gases). The model also exhibits good predictive power regarding the rate of transport of gases through the lungs. Associating the generations with the physical locations in the lungs, using this model, one could predict the radioactive gas distribution patterns in the lung. This could in turn be used to study the obstructive diseases of the lungs. Due to the compartmentalization the model can quite easily be

adopted to include other processes occurring in the lungs such as the obstruction of airways (i.e., by decreasing the radius of the airway).

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