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Modeling and Moments of Multibreath Lung Washout

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Ventilation inhomogeneity, an important characteristic of abnormal lungs, is demonstrated in the dynamics of multibreath lung washout. Quantitative evaluation of the washout curve can be obtained from a model-free index, such as a moment ratio, or parameters of a model. Although a moment ratio is easier to compute and less dependent on noise, the parameters of an appropriate model have a direct physiological interpretation. In this study, we develop an N-alveolar-space model from dynamic mass balance equations, which account for breathing pattern variations. The general model takes the form of a set of time-varying, linear difference equations. Special cases of fewer alveolar spaces and time-invariance are examined in more detail. Properties of the time-invariant model are determined with the use of generating functions. In particular, from the generating function of the two-alveolar-space model, the ratio of the first-to-zero moments is expressed in terms of model parameters. If one of the spaces is poorly ventilated, the moment ratio approximately equals the relative volume–flow ratio of that space. As obtained from the model and found experimentally, the moment ratio gets larger as the ventilation inhomogeneity increases.

INTRODUCTION

An important characteristic of abnormal lung function is ventilation inhomogeneity. The degree of this inhomogeneity can be evaluated by a washout of nitrogen (N_2) from the lung (Bouhuys, 1977). A multibreath washout can be used for subjects breathing spontaneously or with mechanical assistance, which require little or no special effort or cooperation. With upright subjects, the multibreath washout is a measure of predominantly intraregional inhomogeneity (Engel and Macklem, 1977). From the N_2 fraction measured continuously at the mouth during the washout, a washout curve can be constructed from the envelope of the N_2 fractions obtained from successive end-tidal expiratory peaks. The washout curve depends not only on ventilation inhomogeneity, but also on the breathing pattern and lung volume. By appropriate scaling, however, the effects of breathing pattern and lung volume variability can be significantly reduced (Saidel *et al.*, 1975).

To quantify the degree of ventilation inhomogeneity, many parameters or indices have been developed. (As used in this paper, a parmeter is a constant in a

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mathematical model which describes an entire system response function. An index is an arbitrary function of some characteristics of a system response function.) For a homogeneously ventilated lung, the single-alveolar-space model of Fowler *et al.* (1952) predicts that the N_2 fraction of the lung should decrease exponentially with breath number. From actual measurements, only washout curves from normal lungs with little ventilation inhomogeneity can be represented by a single exponential. As the ventilation inhomogeneity in lungs becomes greater, deviations from the single exponential model become more noticeable. Consequently, general models of washout involve more than one alveolar space. These models may be derived from compartmental mass balances or arbitrarily specified in an algebraic form, such as a sum of exponentials. Common independent variables of such models are discrete breath number and continuous time.

A model of two exponentials in time, such as that by Chiang and Yang (1975), contains four parameters. Nakamura *et al.* (1968) deal with a sum of an arbitrarily large number of exponentials which is taken to the continuous limit. By using an arbitrarily large number of compartments in parallel, Gomez *et al.* (1964) and Lecocq (1976) also take the model solution to the continuous limit. Models developed from compartments in series and parallel have been presented by Saidel *et al.* (1971) and Paiva and Demeester (1971). The former model consists of five perfectly mixed compartments in which the N_2 concentrations, derived from balance equations, are continuous functions of time. The model by Paiva and Demeester has up to 31 compartments. As more compartments are added, the number of parameters to be estimated increases significantly. For clinical purposes, however, models proposed to date are not practical. These models involve many parameters which cannot be readily or uniquely evaluated. Furthermore, most of these models cannot take into account the effects of breathing pattern variability, especially on a breath-by-breath basis.

A number of indices have been reported for clinical use that are normalized with respect to an idealized lung model with a single alveolar space. This model is incorporated in the following indices: Bates and Christie (1950) Index, ventilatory efficiency (Prowse and Cumming, 1973), mixing ratio (Edelman, 1968), index of alveolar ventilation (Lichtneckert and Lundgren, 1963), five-breath index (Weygandt, 1976).

Other clinical indices are not normalized with any mathematical model. Cournand *et al.* (1941) used the N_2 fraction in the lung at the end of the 7 min, which is usually greater in emphysematous than in normal lungs, as an index of ventilation inhomogeneity. Other "model-free" indices are related to the number of volume turnovers: the Becklake (1952) Index and the lung clearance index (Bouhuys, 1963).

Typically, clinical indices are simple to compute, but they cannot be used to detect mild ventilation inhomogeneity nor distinguish among various disease states (Fleming *et al.*, 1977). For the most part, these indices do not provide appropriate scaling for breathing pattern variation and lung size differences. Often an index is computed from one sample data point, which inherently leads to poor reproducibility. To minimize these problems, Saidel *et al.* (1975) presented a scaling and moment analysis procedure of the multibreath N_2 washout curve.

Moment ratios (indices) are found to be highly reproducible, and differentiate well among mild, moderate, and severe ventilation inhomogeneity (Fleming *et al.*, 1977).

Here, we shall present an interpretation of the moments in terms of parameters of a two-alveolar-compartment model. Since a model itself may provide useful parameters for characterizing ventilation inhomogeneity, we shall develop it in a way which allows for changes in the breathing pattern and differences in lung size. In the following section, we shall present a discrete-time, mass-balance model with multiple alveolar compartments. The characteristics of this model and the special case of two alveolar compartments will be examined.

MULTIALVEOLAR SPACE MODEL

Data from multibreath washout can be most suitably incorporated into a multi-alveolar-space model (Fig. 1). Between the environment and the perfectly mixed alveolar spaces, plug transport occurs through a constant volume dead space. From the integrated mass balances equations of the alveolar spaces, we can derive a discrete-time, lumped-parameter model.

If the gas density is constant, the total mass balance over alveolar space i reduces to

$$dV_i/dt = Q_i, \qquad i = 2, 3, \ldots, N+1, \tag{1}$$

where V_i is the volume and Q_i is the flow rate. Let us assume that a constant flow fraction, $f_i = Q_i/Q$, exists such that

$$\sum_{i=2}^{N+1} f_i = 1. \tag{2}$$

Upon integration of Eq. (1), the volume $V_i(K, I)$ at the end of inspiration K

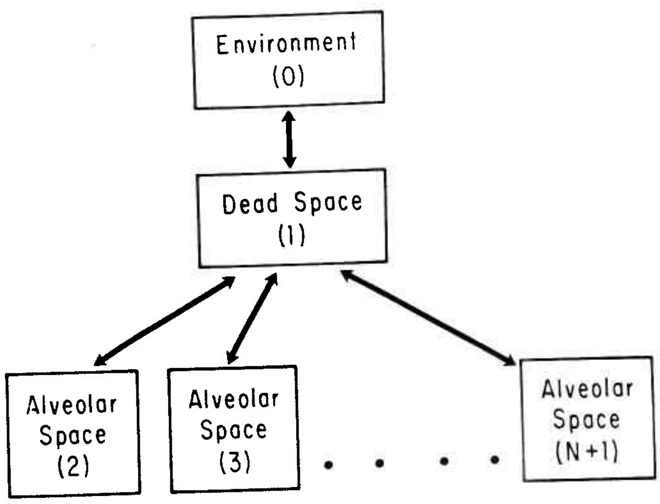

FIG. 1. Multi-alveolar-space model.

can be related to the volume $V_i(K-1, E)$ at the end of expiration $K-1$:

$$V_i(K, I) = V_i(K-1, E) + f_i \Delta V(K, I), \tag{3}$$

where $\Delta V(K, I)$ is the lung volume change over the inspiration K. Summing Eq. (3) over all alveolar spaces, $i = 2, 3, \ldots, N+1$, we find

$$V_A(K, I) = V_A(K-1, E) + \Delta V(K, I), \tag{4}$$

where V_A is the total alveolar volume. Next, let us assume that the alveolar volume fractions at the end of inspiration and expiration are constants:

$$v_i(\tau) = V_i(K, \tau)/V_A(K, \tau), \tag{5}$$

where $V_A(K, \tau)$ is the alveolar volume at the end of the Kth inspiration ($\tau = I$) or expiration ($\tau = E$) and

$$\sum_{i=2}^{N+1} v_i(\tau) = 1. \tag{6}$$

The parameters $v_i(I)$, $v_i(E)$, and f_i can be related by combining Eqs. (3) and (5):

$$v_i(I) V_A(K, I) = v_i(E) V_A(K-1, E) + f_i \Delta V(K, I). \tag{7}$$

The species mass balance for an inert, insoluble gas (e.g., nitrogen) in alveolar space i can be written as

$$\begin{aligned} d[C_i V_i]/dt &= C_{1i} Q_1, \qquad Q_i > 0 \text{ (inspiration)}, \\ &= C_i Q_i, \qquad Q_i < 0 \text{ (expiration)}, \end{aligned} \tag{8}$$

where C_i is the species concentration in alveolar space i and C_{1i} is the species concentration that enters alveolar space i from the dead space. During expiration, the combination of Eqs. (1) and (8) yields

$$V_i \frac{dC_i}{dt} = 0 \Rightarrow C_i(K, E) - C_i(K, I) = 0. \tag{9}$$

That is, the concentration C_i does not change between the end of inspiration K and the end of expiration K. For $|\Delta V| > V_D$, the species mass flow rate leaving the lung is

$$C_{10}(K) Q = \sum_{i=2}^{N+1} Q_i C_i(K, E), \qquad K = 1, 2, \ldots.$$

Upon substitution of the flow fraction, we get the species concentration leaving the lung:

$$C_{10}(K) = \sum_{i=2}^{N+1} f_i C_i(K, E). \tag{10}$$

During inspiration K, the concentration C_{1i} is piecewise constant:

$$\begin{aligned} C_{1i} &= C_{10}(K-1, E), \qquad \Delta V < V_D, \\ &= C_{01}, \qquad \Delta V > V_D, \end{aligned}$$

where C_{01} is the constant input concentration from the environment into the dead space. From integration of the species balance (8) and introduction of the flow fraction, we obtain the difference between the species mass in alveolar space i at the end of inspiration K and end of expiration $K-1$, that is for $\Delta V > V_D$,

$$C_i(K, I)V_i(K, I) - C_i(K-1, E)V_i(K-1, E) = f_i[\Delta V(K, I) - V_D]C_{01} + f_i V_D C_{10}(K-1). \quad (11)$$

The terms on the right are the species mass that enters alveolar space i on inspiration K from the environment and dead space, respectively. Combining Eqs. (7), (9), and (11), we get

$$C_i(K, E) - C_{01} = \alpha_i(K)[C_i(K-1, E) - C_{01}] + \beta_i(K)[C_{10}(K-1) - C_{01}], \quad (12)$$

where

$$\alpha_i(K) = 1 - \phi_i \Delta V(K, I)/V_A(K, I),$$
$$\beta_i(K) = \phi_i V_D/V_A(K, I),$$
$$\phi_i = f_i/v_i(I).$$

In this model the parameters f_i and ϕ_i characterize the distribution of ventilation. Taking these parameters as constants implies that mechanical properties of the lung are invariant. Note that the combination of Eqs. (2), (6), and (7) requires α_i and β_i to lie in the interval (0, 1).

If we define the dimensionless concentrations,

$$X_i(K) = \frac{C_i(K, E) - C_{01}}{C_{10}(0) - C_{01}}, \qquad Y(K) = \frac{C_{10}(K) - C_{01}}{C_{10}(0) - C_{01}},$$

then the multi-alveolar-space model (for $i = 2, 3, \ldots, N+1$) becomes

$$X_i(K+1) = \alpha_i(K)X_i(K) + \beta_i(K)Y(K), \quad (13)$$

$$Y(K) = \sum_{i=2}^{N+1} f_i X_i(K), \quad (14)$$

with the initial conditions $Y(0) = X_i(0) = 1$. For this linear, discrete-time model, the time-varying coefficients ($\alpha_i(k)$ and $\beta_i(k)$) take into account the volume variations, $\Delta V(K, I)$ and $V_A(K, I)$, on each breath. This feature of the model is not incorporated *ad hoc*, but arises naturally through the mass balance relationships. This multi-alveolar model allows for such volume variability, which is essential in the estimation of model parameters using experiment washout data obtained from subjects breathing spontaneously (Saniie, 1977).

REDUCTION OF MODEL DIMENSION

The ratio of flow fraction to alveolar volume fraction, ϕ_i, is the key independent parameter of the multi-alveolar-space model. By setting this ratio equal for any two alveolar spaces p and q ($p \neq q$), the number of alveolar spaces can be reduced from N to $N - 1$. For

$$\phi_p = \phi_q,$$

we find

$$\alpha_p(K) = \alpha_q(K), \qquad \beta_p(K) = \beta_q(K).$$

With these relationships, Eq. (13) yields

$$X_p(K+1) - X_q(K+1) = \alpha[X_p(K) - X_q(K)]. \tag{15}$$

For $X_p(0) = X_q(0) = 1$, Eq. (15) implies

$$X_p(K) = X_q(K) \equiv X(K). \tag{16}$$

Substituting this equality into Eq. (14), we find:

$$Y(K) = \sum_{\substack{i=2 \\ i \neq p,q}}^{N+1} f_i X_i(K) + f_{pq} X(K), \tag{17}$$

where $f_{pq} \equiv f_p + f_q$. Consequently, the number of alveolar spaces and independent parameters is reduced to $N - 1$.

By extension, one can show that for a uniform flow–volume distribution with all alveolar spaces, i.e.,

$$\phi_2 = \phi_3 = \cdots = \phi_{N+1},$$

the constraints of Eqs. (2) and (6) imply

$$\phi_i = 1, \qquad i = 2, 3, \ldots, N+1.$$

In this case, the coefficients $\alpha_i(K)$ and $\beta_i(K)$ become the same for all alveolar spaces:

$$\alpha_i(K) \equiv \alpha(K) = 1 - \Delta V(K, I)/V_A(K, I),$$
$$\beta_i(K) \equiv \beta(K) = V_D/V_A(K, I).$$

Now, multiplication of Eq. (13) by f_i and summation over all i allows us to write Eq. (14) as

$$Y(K+1) = [\alpha(K) + \beta(K)]Y(K). \tag{18}$$

The model acts as if it has two alveolar spaces, when only two of the ratios are independent. In this case, we can write for $i = 2, 3, \ldots, M < N + 1$

$$\phi_i = \phi_p \Rightarrow \alpha_i(K) = \alpha_p(K), \qquad \beta_i(K) = \beta_p(K),$$

and for $i = M+1, M+2, \ldots, N+1$

$$\phi_i = \phi_q \Rightarrow \alpha_i(K) = \alpha_q(K), \qquad \beta_i(K) = \beta_q(K).$$

Consequently, the model for two distinguishable alveolar spaces is given by:

$$X_i(K+1) = \alpha_i(K)X_i(K) + \beta_i(K)Y(K); \qquad X_i(0) = 1; \quad i = p, q, \tag{19a}$$

$$Y(K) = f_p X_p(K) + f_q X_q(K); \qquad X(0) = 1, \tag{19b}$$

where

$$f_p = \sum_{i=2}^{M} f_i \qquad \text{and} \qquad f_q = \sum_{i=M+1}^{N+1} f_i.$$

The two-alveolar-space model, Eqs. (19a), (19b), is the simplest one that can deal with ventilation inhomogeneity. For application to the analysis of experimental washout data, models with more alveolar compartments have too many independent parameters. Consequently, the use of models with more than two alveolar spaces has the disadvantage that the estimated parameter values may not be unique.

TIME-INVARIANT ANALYSIS

To examine the characteristics of the N-alveolar-compartment model, Eq. (19), directly by analytical techniques, we shall deal with the special case of a periodic breathing pattern such that

$$\Delta V(K, I) = \Delta V(K, E) = V_{\mathrm{T}}, \qquad V_{\mathrm{A}}(K, E) = V_{\mathrm{A}}, \qquad V_{\mathrm{A}}(K, I) = V_{\mathrm{A}} + V_{\mathrm{T}}.$$

Consequently, the coefficients of the model are given by:

$$\alpha_i = 1 - \phi_i V_{\mathrm{T}}/(V_{\mathrm{A}} + V_{\mathrm{T}}), \qquad \beta_i = \phi_i V_{\mathrm{D}}/(V_{\mathrm{A}} + V_{\mathrm{T}}).$$

This means that the model reduces to a set of time-invariant, linear difference equations for $i = 2, 3, \ldots, N+1$:

$$X_i(K+1) = \alpha_i X_i(K) + \beta_i Y(K),$$
$$Y(K) = \sum_{i=2}^{N+1} f_i X_i(K). \tag{20}$$

To study this set of linear difference equations, we transform the functions of the discrete breath number, k, into functions of a continuous variable z. Specifically, we introduce the generating functions (Bailey, 1964), which are similar to Z transforms,

$$H_i = \sum_{K=0}^{\infty} X_i(K) Z^K, \qquad G = \sum_{K=0}^{\infty} Y(K) Z^K.$$

In terms of these functions, the problem becomes

$$Z^{-1}[H_i - 1] = \alpha_i H_i + \beta_i G, \qquad i = 2, 3, \ldots, N+1,$$
$$G = \sum_{i=2}^{N+1} f_i H_i.$$

The solution for G is given by

$$G = \sum_{i=2}^{N+1} f_i (1 - \alpha_i Z)^{-1} / [1 - Z \sum_{i=2}^{N+1} f_i \beta_i (1 - \alpha_i Z)^{-1}].$$

Upon rearrangement, this becomes

$$G = \sum_{i=2}^{N+1} [f_i \prod_{\substack{j=2 \\ j \neq i}}^{N+1} (1 - \alpha_j Z)] / [\prod_{i=2}^{N+1} (1 - \alpha_i Z) - Z \sum_{i=2}^{N+1} (f_i \beta_i \prod_{\substack{j=2 \\ j \neq i}}^{N+1} (1 - \alpha_j Z))]. \tag{21}$$

The numerator of the generating function is a polynomial of order $N - 1$ and the denominator is a polynomial of order N. Generally, G can be presented in the form

$$G = \sum_{i=2}^{N+1} q_i/(1 - Zp_i) = \sum_{i=2}^{N+1} q_i \sum_{k=0}^{\infty} (p_i Z)^k, \tag{22}$$

where p_i and q_i are nonlinear functions. By comparison of Eq. (22) to the definition of the generating function G, we find the solution for normalized end-tidal nitrogen fraction is the summation of N different exponential decay functions:

$$Y(K) = \sum_{i=2}^{N+1} q_i p_i^k = \sum_{i=2}^{N+1} q_i \exp(K \ln p_i). \tag{23}$$

That the p_i are less than unity is shown for the case of two alveolar spaces in the Appendix. For a single alveolar space, the generating function simplifies to

$$G = \frac{1}{1 - Z(\alpha + \beta)} \equiv \sum_{K=0}^{\infty} (\alpha + \beta)^K \cdot Z^K,$$

where

$$\alpha = V_A/(V_A + V_T), \qquad \beta = V_D/(V_A + V_T).$$

Comparing the above equation to the definition of the (generating function) transform, we see that

$$Y(K) = [\alpha + \beta]^K = [(V_A + V_D)/(V_A + V_T)]^K.$$

This is the expression for washout of an inert gas from a uniformly ventilated lung presented by Fowler *et al.* (1952).

With two independent alveolar spaces, the generating function becomes

$$G = (1 - cZ)/(aZ^2 - bZ + 1), \tag{24}$$

where

$$a = \alpha_2\alpha_3 + f_2\beta_2\alpha_3 + f_3\beta_3\alpha_2,$$
$$b = \alpha_2 + \alpha_3 + f_2\beta_2 + f_3\beta_3,$$
$$c = f_2\alpha_3 + f_3\alpha_2.$$

The formal solution $Y(k)$ for the two-alveolar space model can be obtained from the inverse of the generating function, Eq. (24), but it would not yield any new insights. Rather, we use the generating function to obtain moments of the multibreath washout curve. Experimentally, we have found that the ratio of first-to-zeroth moments provides an index of ventilation inhomogeneity which is superior to others in the literature (Fleming *et al.*, 1977). What remains to be shown is how this moment ratio can be interpreted in terms of parameters of a suitable physiological model.

MOMENTS RELATED TO MODEL PARAMETERS

A partial system identification of the lung with respect to transport and mixing in the pulmonary gas spaces can be obtained from the first few moments of the multibreath washout response function, i.e., the sequence of normalized end-tidal concentrations (Saidel *et al.*, 1975). Although moment ratios yield a model-free characterization of the multibreath washout curve, a model basis of the moments would help to understand them in more common physiological terms. The simplest inhomogeneous model having two distinct alveolar spaces is adequate for this purpose.

The rth moment of $Y(K)$, the dimensionless end-tidal concentration as a function of breadth number, is given by

$$\lambda_r = \sum_{K=0}^{\infty} K^r Y(K); \qquad r = 0, 1, 2, \ldots.$$

Of particular interest is the moment ratio λ_1/λ_0, which is the mean breath number of the washout response function. From the transform function defined as

$$G(Z) = \sum_{K=0}^{\infty} Z^K Y(K),$$

the moments can be determined from successive derivatives, e.g.,

$$\lambda_0 = G(1), \qquad \lambda_1 = \left.\frac{dG}{dZ}\right|_{Z=1}.$$

For the simplest time-invariant model with one alveolar space, we find

$$G(Z) = [1 - Z(V_A + V_D)/(V_A + V_T)]^{-1}.$$

The mean breath number is

$$\lambda_1/\lambda_0 = (V_A + V_D)/(V_T - V_D) = FRC/(V_T - V_D).$$

To eliminate FRC and reduce the effect of V_T on the moment ratio, one can express the dimensionless end-tidal concentration as a function of a dilution number (Saidel *et al.*, 1975). The dilution number, defined as the ratio of cumulative expired volume divided by FRC, is for the time invariant model simply

$$\eta_K = K \cdot V_T/FRC.$$

The moments using this independent variable are given by

$$\mu_r = \sum_{K=0}^{\infty} \eta_K{}^r \cdot Y(\eta_K)[\eta_K - \eta_{K-1}] = (V_T/FRC)^{r+1}\lambda_r.$$

Consequently, for the one-alveolar-space model, the mean dilution number, μ_1/μ_0, is independent of FRC:

$$\frac{\mu_1}{\mu_0} = \frac{V_T}{FRC}\frac{\lambda_1}{\lambda_0} = \frac{V_T}{V_T - V_D}. \tag{25}$$

When $V_T \gg V_D$, the mean dilution number is close to unity and nearly independent of V_T and V_D.

Moments of the two-alveolar-space model are not simply related to model parameters. From Eq. (24) and its derivative, we obtain the moment ratio

$$\frac{\lambda_1}{\lambda_0} = \frac{1-a}{a-b+1} - \frac{1}{1-c} = \frac{1}{\gamma}\left[\frac{\delta - \gamma(\gamma-\delta)}{\gamma-\delta} + \frac{1}{\phi_2} + \frac{1}{\phi_3} - \frac{1}{\phi_2\phi_3}\right], \quad (26)$$

where

$$\gamma = V_T/(V_A + V_T), \qquad \delta = V_D/(V_A + V_T).$$

For uniform ventilation ($\phi_2 = \phi_3 = 1$), this moment ratio reduces properly to the one-alveolar-space model. For nonuniform ventilation ($\phi_2 \neq \phi_3 \neq 1$),

$$1/\phi_2 + 1/\phi_3 - 1/\phi_2\phi_3 > 1, \quad (27)$$

which implies than λ_1/λ_0 is larger as the ventilation inhomogeneity becomes greater. Typically, one would expect the first term in the brackets of Eq. (26) to be of the order of 10^{-1}. In the presence of significant ventilation inhomogeneity such that the term involving γ and δ is small compared to the terms involving ϕ_2 and ϕ_3, we find from Eqs. (25) and (26)

$$\mu_1/\mu_0 \simeq 1/\phi_2 + 1/\phi_3 - 1/\phi_2\phi_3. \quad (28)$$

This shows that the moment ratio is indicative of abnormal flow–volume ratios.

By definition of the parameters, we find

$$\phi_i = \left[\frac{1}{f_j} - 1\right] \Big/ \left[\frac{1}{f_j} - \frac{1}{\phi_j}\right], \qquad i, j = 2, 3, i \neq j.$$

We see for $0 < \phi_i < \infty$ that $\phi_j > f_j$. In the special case of $f_j \ll 1$,

$$\phi_i \simeq 1/[1 - f_j/\phi_j].$$

For this case, as ϕ_j approaches f_j, ϕ_i increases without bound; hence, Eq. (28) reduces to

$$\mu_1/\mu_0 \simeq 1/\phi_j = v_j/f_j. \quad (29)$$

From Eq. (29) the moment ratio for this ventilation inhomogeneity can be interpreted simply as the volume–flow ratio of the poorly ventilated space.

SUMMARY

A multi-alveolar-space model is developed for pulmonary washout of an inert gas species over many breaths. The model is formulated using mass balance equations which allow variable volume changes to occur on each breath. This is of value in the analysis of experimental washout data from subjects breathing spontaneously. In the model, ventilation inhomogeneity is characterized by the relative distributions of flow and volume associated with the alveolar spaces. For the special case of a constant, periodic breathing pattern, the model equations are solved using generating function transformations of the end-tidal species fractions. Also, the generating function of the end-tidal fractions exhaled yields moments of the washout curve. In particular, we examine the moments of the

two-alveolar-space model. When the washout curve is expressed in terms of dilution number (or volume turnovers), the ratio of the first-to-zeroth moments (or mean dilution number) is relatively insensitive to changes in lung volume, tidal volume, and dead space volume; it depends primarily on alveolar flow-volume distribution. As the ventilation inhomogeneity increases, the mean dilution number is approximately the ratio of volume-to-flow fractions of the poorly ventilated alveolar space.

APPENDIX

The generating function for two alveolar spaces can be expressed in partial fractions as

$$G = \sum_{i=1}^{2} q_i/(1 - Zp_i).$$

With reference to Eq. (24) in the text, the functions q_i and p_i can be defined as:

$$p_1 = 2a/[b + (b^2 - 4a)^{\frac{1}{2}}], \qquad p_2 = 2a/[b - (b^2 - 4a)^{\frac{1}{2}}],$$
$$q_1 = (p_1 - c)/(p_1 - p_2), \qquad q_2 = (p_2 - c)/(p_2 - p_1).$$

Since

$$b^2 - 4a = (\alpha_2 - \alpha_3 + f_2\beta_2 + f_3\beta_3)^2 + 4f_2f_3\beta_2\beta_3 > 0,$$

and

$$b \pm (b^2 - 4a)^{\frac{1}{2}} > 0,$$

we see that $p_2 > p_1 > 0$. If $p_2 < 1$, then $p_1 < 1$ and the washout curve as given by Eq. (23) in the text is simply a summation of two distinct exponential decay curves. Proving that $p_2 > 1$ is equivalent to proving

$$2a < b - (b^2 - 4a)^{\frac{1}{2}} \Rightarrow a - b + 1 > 0.$$

From the definitions given above, we find

$$a - b + 1 = \phi_2\phi_3\gamma[\gamma - \delta],$$

where

$$\gamma = V_T/(V_A + V_T), \qquad \delta = V_D/(V_A + V_T).$$

Since ϕ_2, ϕ_3, γ, and $\gamma - \delta$ are positive, we find $p_2 < 1$.

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