COMPUTERS AND BIOMEDICAL RESEARCH 13, 446–457 (1980)

Lung Washout during Spontaneous Breathing: Parameter Estimation with a Time-Varying Model*

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Received June 11, 1979

We use a time-varying model to analyze the multibreath washout of nitrogen from lungs of human subjects breathing spontaneously. Based on standard pulmonary function evaluation, the 39 subjects tested are classified in the following categories: nonsmoking normal, "smoking" normal, asthma, diffuse interstitial lung disease, and chronic obstructive lung disease. The degree of ventilation inhomogeneity among these subjects was indicated by two independent parameters of the model, which were estimated by nonlinear optimization. A Gauss–Newton algorithm with a Marquardt modification was applied to a least-squares objective function. Constraints were included in a penalty function. Values of the model parameters from repeated washouts of the same subjects showed wide variability. Also, model parameters did not appear to provide any better distinction among clinical groups than did a moment ratio whose computation is much less expensive and more reliable.

INTRODUCTION

Information on ventilation inhomogeneity can be obtained from a lung washout (or washin) experiment with an inert and slightly soluble gas species such as nitrogen. The degree of ventilation inhomogeneity is an important

* Supported in part by the Medical Research Service of the Veterans Administration. J. Saniie received a summer fellowship from the Northern Ohio Lung Association.

0010-4809/80/050446-12$02.00/0

characteristic of abnormal pulmonary function, which may be present in many disease states. For subjects who cannot or will not breath according to a specified maneuver, a multibreath washout during spontaneous breathing can yield information sufficient to quantify the degree of ventilation inhomogeneity from mild to severe. For most clinical purposes, one would like a single quantitative measure of ventilation inhomogeneity which is relatively easy to compute. As a consequence, many indices that are ad hoc functions of the washout data have been proposed (*1, 2*). Typically, such indices do not detect mild ventilation inhomogeneity nor distinguish its severity among various disease states. An exception is the moment ratio developed by Saidel *et al.* (*3*) which was applied to washout with spontaneous breathing (*4*) and compared to other indices (*5*).

Another approach taken to the assessment of ventilation inhomogeneity is through modeling and parameter estimation (*6, 7*). For the most part, such models assume invariant breathing patterns and have too many parameters for efficient and unique estimation. In the present study, using a model which does permit time-varying breathing patterns, we examined the sensitivity and intrasubject variability of the parameter estimates in subjects with normal lungs or in various disease states.

TIME-VARYING MODEL

To describe the multibreath washout of nitrogen from the lungs, we use a two-alveolar compartment model (Fig. 1) which is a special case of our more general model (*8*). Between the airway opening and the perfectly mixed alveolar spaces, plug transport occurs through a constant volume dead space. The model equations are derived from integrated mass balances of the alveolar spaces, assuming negligible changes in gas density and no significant alveolar–capillary transport of nitrogen. Consequently, we obtain a discrete, time-varying, linear model. In dimensionless form, for breaths $k = 1, 2, 3, \ldots$ and alveolar spaces $i = 2, 3$, the model equations are

$$X_i(k) = \alpha_i(k-1)X_i(k-1) + \beta_i(k-1)Y(k-1), \quad [1]$$

and

$$Y(k) = f_2X_2(k) + f_3X_3(k). \quad [2]$$

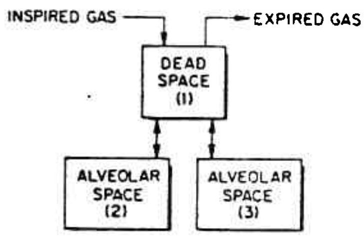

FIG. 1. Schematic of lung model structure.

At the end of breath k, $X_i(k)$ is the dimensionless nitrogen fraction in alveolar space i, and $Y(k)$ is the dimensionless nitrogen fraction leaving the lungs. Initially, $X_i(0) = Y(0) = 1$. The time-varying coefficients for each alveolar space are

$$\alpha_i(k) = 1 - \phi_i \Delta V(k, I)/V_A(k, I) > 0 \quad [3]$$

and

$$\beta_i(k) = \phi_i V_D/V_A(k, I) > 0, \quad [4]$$

where $\Delta V(k, I)$ is the lung volume change on the kth inhalation, $V_A(k, I)$ is the total alveolar volume at the end of the kth inhalation, and V_D is the dead space volume. Under physiological conditions, these volumes obey the following inequalities:

$$V_A(k, I) > \Delta V(k, I) > V_D. \quad [5]$$

Since these volumes can be computed directly from experimental data or estimated by use of mass balances, they can be regarded as known.

The parameters f_i and ϕ_i characterize distributions associated with the alveolar spaces. The fraction f_i of flow entering or leaving alveolar space i relative to the volume fraction v_i of alveolar space i, that is ϕ_i, indicates the uniformity of ventilation. By definition, for $i, j = 2, 3$ and $i \neq j$,

$$\phi_i = f_i/v_i = (1 - f_j)/(1 - f_j/\phi_j) > 0, \quad [6]$$

$$f_i = 1 - f_j > 0, \quad [7]$$

and

$$v_i = 1 - v_j > 0. \quad [8]$$

Because of these relations, only two parameters are independent. For the special case $\phi_i = 1$, which implies a uniform ventilation distribution, one can show that the two-space model degenerates into a one-space model (*8*).

With the two-space model, however, we do not have unique solutions. Arbitrarily, let us take f_2 and v_2 as the independent parameters and write the output of the model as

$$\begin{aligned} Y(k) = {} & f_2\{X_2(k-1) - (f_2/v_2)[a(k-1)X_2(k-1) + b(k-1)Y(k-1)]\} \\ & + f_3\{X_3(k-1) - (f_3/v_3)[a(k-1)X_3(k-1) + b(k-1)Y(k-1)]\}, \end{aligned}$$

where $a(k) \equiv \Delta V(k, I)/V_A(k, I)$ and $b(k) \equiv V_D/V_A(k, I)$. Starting with $Y(0) = X_2(0) = X_3(0)$, we see that for values $k = 1, 2, \ldots$ the solution is unaltered by the interchange of parameters

$$\begin{Bmatrix} v_2 \\ f_2 \end{Bmatrix} \Leftrightarrow \begin{Bmatrix} v_3 = 1 - v_2 \\ f_2 = 1 - f_3 \end{Bmatrix}.$$

Thus, if $f_2 = u$ and $v_2 = w$ yields a solution, then $f_2 = 1 - u$ and $v_2 = 1 - w$ will yield the identical solution (Fig. 2). From the equation for a straight line

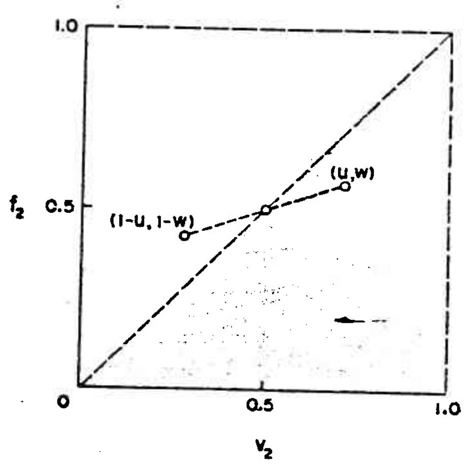

FIG. 2. Feasible region of the parameter space.

between these points,

$$\frac{f_2 - u}{v_2 - w} = \frac{f_2 - (1 - u)}{v_2 - (1 - w)} \Rightarrow f_2 = v_2 = 0.5,$$

we see that all solutions symmetric about (0.5, 0.5) are equivalent. Also, along the line $f_2 = v_2$ (or $\phi_2 = 1$), an infinity of parameter values yields the same solution. One way to assure a unique solution is to limit the parameter space to the region

$$\phi_2 = f_2/v_2 < 1. \qquad [9]$$

In addition to this constraint, the flow fraction parameter must lie in the interval

$$0 < f_2 < 1. \qquad [10]$$

Finally, from the definitions and equalities [3]–[10], we find that on any breath k,

$$0 < f_2 < \phi_2[1 - (1 - f_2)\Delta V(k, I)/V_A(k, I)] < \phi_2 < 1. \qquad [11]$$

EXPERIMENTAL METHODS

Subjects inhaled humidified oxygen and exhaled to the environment to wash nitrogen from the lungs over a number of breaths. The subjects included 7 normal nonsmokers, 5 "normal" smokers, 6 with asthma, 11 with diffuse interstitial lung disease, and 10 with chronic obstructive pulmonary disease. Pulmonary function of subjects was assessed by spirometry and body plethysmography. Each subject performed the washout twice with relaxed and spontaneous breathing. At the mouth, the nitrogen fraction and flow rate were measured continuously and analyzed by digital computer (*4*).

The nitrogen and flow signals were sampled at 40 Hz. These digitized data were filtered and calibrated with compensation for delay time, gas composition, and temperature. Lung volume change (ΔV) on inhalation and exhalation was obtained by integrating the preprocessed flow signal. The nitrogen fraction at the end of each breath and the average nitrogen fraction exhaled on each breath were computed. With these variables, mass balance equations were used to estimate the resting lung volume (FRC) and the dead-space volume (V_D). From the total alveolar volume at rest (V_A = FRC $-$ V_D) and the volume changes during each breath, we were able to evaluate the alveolar volume at the end of each inhalation and exhalation.

Moment Analysis

Experimental studies (*4*) show that a moment analysis of the washout data yields a simple but sensitive and reliable index of ventilation inhomogeneity. This index is the ratio of first-to-zeroth moments, μ_1/μ_0, where

$$\mu_r = \sum_k \eta_k{}^r Y(k)[\eta_k - \eta_{k-1}], \qquad r = 0, 1.$$

The independent variable, η_k, is the cumulative expired volume at the end of breath k divided by the initial resting lung volume (FRC). In the special case of a time-invariant breathing pattern, we can relate the parameters of the model to moments of the washout (*8*). It turns out that

$$\mu_1/\mu_0 = \omega[1/\phi_2 + 1/\phi_2 + 1/\phi_2\phi_3],$$

where the proportionality coefficient, ω, depends on V_D, V_A, and ΔV. To justify the use of model analysis, we need to show that it can yield reliable information not available in the moment ratio.

Parameter Estimation

For each experimental washout curve appropriately processed, we can obtain the normalized nitrogen fraction $Y_d(k)$ leaving the lungs at the end of successive breaths. The parameter values that provide the best fit of the model output $Y(k)$ to $Y_d(k)$ characterize ventilation inhomogeneity of the lungs washed out. As a best-fit criterion, we choose to minimize the residuals in a least-squares sense:

$$\Phi_{LS} = \sum_{k=1}^{n} [Y_d(k) - Y(k)]^2.$$

Since the outputs, $Y_d(k)$, are suitably scaled and the effects of measurement error on different breaths is essentially random, no weighting matrix is introduced. Linear regression is not applicable because the parameters f_i and ϕ_i appear as products in the model. Consequently, an iterative algorithm is used to minimize Φ_{LS}.

To help keep the iterative procedure within the feasible parameter space, we introduce inequality constraints in a penalty function. Consequently, the complete objective function to be minimized is

$$\Phi = \Phi_{LS} + \gamma\Phi_{PF}, \quad [12]$$

where the penalty function is

$$\Phi_{PF} = \sum_{j=1}^{3} 1/hj. \quad [13]$$

The constraint functions $h_j > 0$ are based on the inequalities given in [11]

$$h_1 = f_2; \quad h_2 = 1 - \phi_2, \quad h_3 = \min_{1 \leq k \leq n} [1 - (1 - f_2)\Delta V(k, I)/V_A(k, I)]\phi_2 - f_2.$$

Only one constraint coefficient γ is needed because in the normalized form of the model, dimensionless variables and parameters typically lie between 0.1 and 1.

The minimum of the objective function is determined by an iterative Gauss–Newton optimization with a Marquardt-type modification (9). The value of the parameter vector $\boldsymbol{\theta} = [f_2, \phi_2]^T$ after iteration i is given by

$$\boldsymbol{\theta}^{i+1} = \boldsymbol{\theta}^i - R^i\mathbf{q}^i,$$

where $\mathbf{q} = \partial\Phi/\partial\boldsymbol{\theta}$ is the gradient vector and $R = [N + \lambda D]^{-1}$ is a modified inverse Hessian matrix. Specifically, N is the approximate Hessian matrix of the objective function which ignores second-order derivatives and D is a diagonal matrix whose diagonal elements are

$$D_{rr} = |N_{rr}| \quad \text{for } N_{rr} \neq 0,$$
$$= 1 \quad \text{for } N_{rr} = 0.$$

A sufficiently large scalar $\lambda > 0$ is chosen to ensure that R is positive definite. Exact forms of q and N are given in the Appendix. At each step of the iteration, we must compute not only the output $Y(k)$ from Eqs. [1] and [2] but also the sensitivity coefficients $\partial Y(k)/\partial f_2$ and $\partial Y(k)/\partial\phi_2$. These terms arise from taking derivatives of the objective function. The sensitivity equations also are given in the Appendix.

The flow chart for the optimization is shown in Fig. 3. Initially, the volumes V_D, $\Delta V(k, I)$, and $V_A(k, I)$ for $k = 1, 2, \ldots n$ are evaluated from the data. We then choose initial parameter values, say, $\boldsymbol{\theta}^0 = [0.3, 0.8]^T$, which easily satisfy the constraints. With this information, the model and sensitivity equations are solved. Since initial parameter values are well within the feasible region, we made the initial value of the penalty function coefficient suitably small, $\gamma = 10^{-3}\ \Phi_{LS}/\Phi_{PF}$. The initial value of the Marquardt coefficient initially is also assumed to be small, $\lambda = 10^{-4}$. After computation of the objective function and its derivatives, the parameter vector is updated and the model and sensitivity equations solved again. If the newly evaluated objective function is not less than the previous one, the Marquardt coefficient is increased; otherwise, the

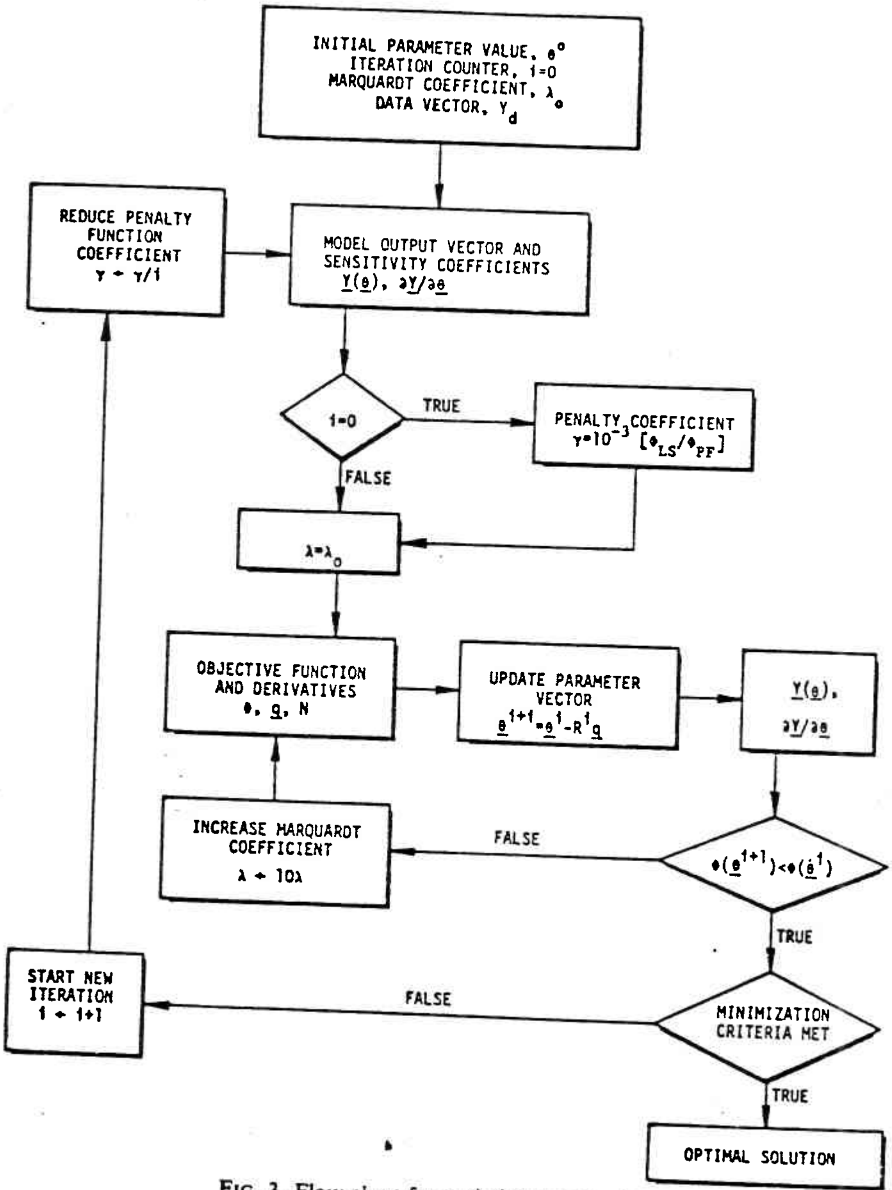

FIG. 3. Flow chart for optimization algorithm.

minimization criteria are applied:

(M.1) $\gamma\Phi_{PF}(\theta^i)/\Phi_{LS}(\theta^i) < 10^{-4}$,
(M.2) $\Phi(\theta^i) - \Phi(\theta^{i+1}) < 10^{-5}$,
(M.3) $|\theta_s^{i+1} - \theta_s^i|/(\theta_s^i + 10^{-4}) < 10^{-3}$,

where

$$\theta_s = f_2, \quad s = 1,$$
$$= \phi_2, \quad s = 2.$$

If these criteria are not satisfied, a new iteration is started with a smaller penalty function coefficient.

To check the suitability of this algorithm, we performed a variety of tests with data generated from the model using different values of the parameters including some very close to the limits imposed by the constraints. Optimizations were repeated with initial estimates of the parameter vector near and far from the known global minimum. Also, studies were made with 5% random noise superposed on the data generated by the model.

Results and Discussion

The parameter estimation algorithm was tested with model-generated data assuming several sets of values for the volumes ΔV, V_A, and V_D and for the parameters f_2 and ϕ_2. Also, the washout was truncated when the output was reduced to 6 or 3% of the initial value ($Y(n) = 0.06$ or 0.03). As long as ϕ_2 was not close to the point of model degeneracy ($\phi_2 = 1$), estimates of both f_2 and ϕ_2 were essentially identical to the true values for different initial parameter estimates, volumes, and truncation points. With the true value of $\phi_2 = 0.999$, estimates of ϕ_2 were almost exact for the various situations, but the estimates of f_2 differed greatly. The effect of different truncation points was not significant. In addition to dealing with ideal noise-free data, we also examined the model-generated data corrupted by random noise that was 5% of the initial output value. The errors produced in both f_2 and ϕ_2 were large and depended upon the other conditions even away from $\phi_2 = 1$.

From the washout of the 39 subjects, we analyzed the sequence of output values truncated at $Y(n) = 0.03$. For these data, the parameters f_2 and ϕ_2 were estimated. If either the number of iterations or the least-squares objective function at the optimal point were unusually large (greater than 50 or 0.04, respectively), the estimates were repeated with different initial guesses. Except for a few cases where the "noise" in the washout appeared to be substantial, the repeated estimates were within a few percent. For each subject, the values of f_2 and ϕ_2 are plotted in Fig. 4. As expected, subjects with chronic obstructive pulmonary disease have the greatest degree of ventilation inhomogeneity. As f_2 becomes more abnormal (smaller) so does ϕ_2. By the inequality relations, f_2 is always less than ϕ_2. Since different values of f_2 and ϕ_2 were obtained for repeated washouts of the same individual, we chose the set having the smallest value of the least-squares objective function.

As a measure of the variability of these parameters, we define a mean relative difference:

$$\mathrm{MRD}(Z) = \sum_{i=1}^{n} \frac{|Z_{1i} - Z_{2i}|}{n(Z_{1i} + Z_{2i})/2},$$

where Z_{ji} is the parameter value of the jth washout of subject i. By this measure, the variability of f_2 is much greater than that of ϕ_2: $\mathrm{MRD}(f_2) = 0.20$ and $\mathrm{MRD}(\phi_2) = 0.12$.

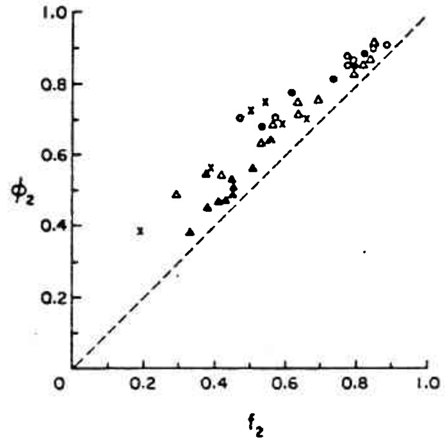

FIG. 4. Estimates of parameters f_2 and ϕ_2 of subjects in five groups: Normal nonsmoking (○), normal smoking (●), asthma (×), diffuse interstitial lung disease (△), chronic obstructive pulmonary disease (▲).

Because the moment ratio μ_1/μ_0 has been found to be a valuable index of ventilation inhomogeneity (*4, 5*), it is worth comparing to model parameters. Figure 5 shows ϕ_2 versus μ_1/μ_0. The larger values of μ_1/μ_0, which indicate greater ventilation inhomogeneity, tend to be associated with smaller values of ϕ_2, as expected. Theoretically, the volume/flow index

$$\text{VFI} \equiv 1/\phi_2 + 1/\phi_3 + 1/\phi_2\phi_3$$

should be proportional to μ_1/μ_0. To some extent this is indicated by the data in Fig. 6. The variability of the VFI is a little smaller than that of the moment ratio: MRD(VFI) = 0.06 and MRD(μ_1/μ_0) = 0.08.

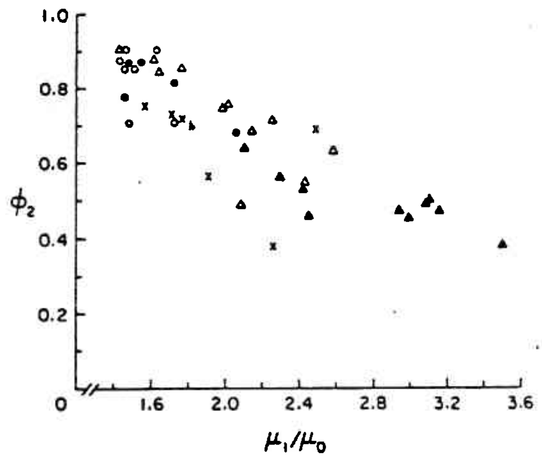

FIG. 5. Comparison of the flow/volume parameter ϕ_2 with the moment ratio μ_1/μ_0 of subjects in five groups. (See legend of Fig. 4.)

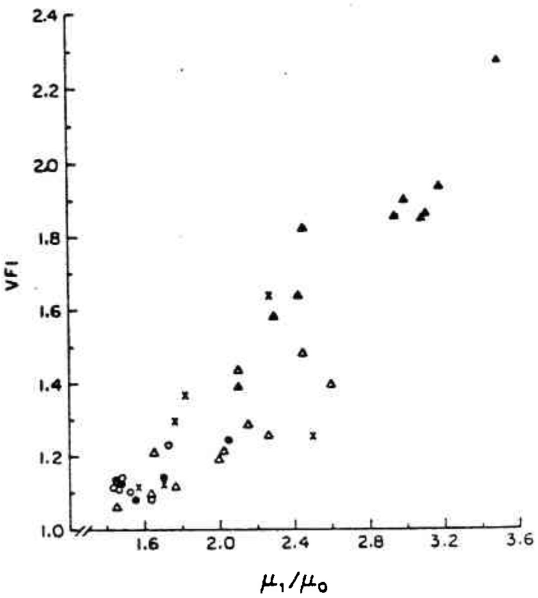

FIG. 6. Comparison of VFI = $1/\phi_2 + 1/\phi_3 = 1/\phi_2\phi_3$ with the moment ratio μ_1/μ_0 of subjects in five groups. (See legend of Fig. 4.)

Not only do the model parameters, f_2 and ϕ_2, have large intrasubject variability compared to μ_1/μ_0 and VFI, but they also fail to provide sufficient distinction among normal, asthmatic, and DILD subjects (Fig. 4). Comparison of ϕ_2 and μ_1/μ_0 shows that the latter does yield more distinction among these clinical groups. Although VFI and μ_1/μ_0 are about the same in terms of variability and distinction among groups, parameter estimation for the VFI has a much greater computational cost than does the moment analysis. Also, it is more likely that the parameter estimation algorithm will be misled by noisy data.

Since a simple two-alveolar space model is subject to problems of uniqueness and ill-determined parameter estimates at the optimal point, a more complex model would be even more prone to these problems. Increasing the number of alveolar spaces to three yields a model with four independent parameters rather than two. Although the model may fit the data more closely, as indicated by a smaller value of the objective function at the optimal point, the parameter values at that point are likely to be even more ill determined.

In conclusion, information that can be obtained from the multibreath washout of nitrogen from the lungs is insufficient to justify the use of a model analysis with parameter estimation. The use of moment analysis is preferable for characterizing ventilation inhomogeneity.

APPENDIX

The gradient vector of the objective function has two elements

$$\mathbf{q} = \begin{bmatrix} \dfrac{\partial \Phi}{\partial f_2} \\ \dfrac{\partial \Phi}{\partial \phi_2} \end{bmatrix} = \begin{bmatrix} -2 \sum_{k=1}^{n} [Y_d(k) - Y(k)] \dfrac{\partial Y(k)}{\partial f_2} - \gamma \sum_{j=1}^{3} \dfrac{\partial h_j}{\partial f_2} \Big/ h_j^2 \\ -2 \sum_{k=1}^{n} [Y_d(k) - Y(k)] \dfrac{\partial Y(k)}{\partial \phi_2} - \gamma \sum_{j=1}^{3} \dfrac{\partial h_j}{\partial \phi_2} \Big/ h_j^2 \end{bmatrix}.$$

The approximate Hessian has four elements

$$N = \begin{bmatrix} N_{11} & N_{12} \\ N_{21} & N_{22} \end{bmatrix} \simeq \begin{bmatrix} \partial^2\Phi/\partial f_2^2 & \partial^2\Phi/\partial f_2 \partial \Phi_2 \\ \partial^2\Phi/\partial \phi_2 \partial f_2 & \partial^2\Phi/\partial \phi_2^2 \end{bmatrix},$$

where

$$N_{11} = 2\left[\sum_{k=1}^{n} \left(\frac{\partial Y(k)}{\partial f_2}\right)^2 + \gamma \sum_{j=1}^{3} \left(\frac{\partial h_j}{\partial f_2}\right)^2 \Big/ h_j^3\right],$$

$$N_{12} = N_{21} = 2\left[\sum_{k=1}^{n} \frac{\partial Y(k)}{\partial f_2} \cdot \frac{\partial Y(k)}{\partial \phi_2} + \gamma \sum_{j=1}^{3} \frac{\partial h_j}{\partial f_2} \cdot \frac{\partial h_j}{\partial \phi_2} \Big/ h_j^3\right],$$

$$N_{22} = 2\left[\sum_{k=1}^{n} \left(\frac{\partial Y(k)}{\partial \phi_2}\right)^2 + \gamma \sum_{j=1}^{3} \left(\frac{\partial h_j}{\partial \phi_2}\right)^2 \Big/ h_j^3\right].$$

The sensitivity equations are the derivatives of the output $[Y(k)]$ and state variables $[X_i(k)]$ with respect to the independent parameters $[f_2, \phi_2]$. For simplicity in writing the derivatives of $Y(k)$, let $\alpha_1(k-1) = 1 - \phi_i \rho$ and $\beta_i(k-1) = \phi_i \sigma$, where $\rho = \Delta V(k-1, I)/V_A(k-1, I)$ and $\sigma = V_D/V_A(k-1, I)$ so that the model equations take the form

$$X_i(k) = X_i(k-1) - \phi_i[\rho X_i(k-1) - \sigma Y(k-1)], \qquad i = 2, 3,$$

$$Y(k) = \sum_{i=2}^{3} f_i X_i(k).$$

Taking the derivatives of the output, we get

$$\frac{\partial Y(k)}{\partial f_2} = \sum_{i=2}^{3} \left[\frac{\partial f_i}{\partial f_2} X_i(k) + f_i \frac{\partial X_i(k)}{\partial f_2}\right],$$

$$\frac{\partial Y(k)}{\partial \phi_2} = \sum_{i=2}^{3} \left[\frac{\partial f_i}{\partial \phi_2} X_i(k) + f_i \frac{\partial X_i(k)}{\partial \phi_2}\right].$$

Now, we need to evaluate the derivatives of the other state variables (X_i)

$$\frac{\partial X_i(k)}{\partial f_2} = \frac{\partial X_i(k-1)}{\partial f_2} - \frac{\partial \phi_i}{\partial f_2} [\rho X_i(k-1) - \sigma Y(k-1)] - \phi_i\left[\rho \frac{\partial X_i(k-1)}{\partial f_2} - \sigma \frac{\partial Y(k-1)}{\partial f_2}\right],$$

$$\frac{\partial X_i(k)}{\partial \phi_2} = \frac{\partial X_i(k-1)}{\partial \phi_2} - \frac{\partial \phi_2}{\partial \phi_2}[\rho X_i(k-1) - \sigma Y(k-1)] - \phi_i\left[\rho \frac{\partial X_i(k-1)}{\partial \phi_2} - \sigma \frac{\partial Y(k-1)}{\partial \phi_2}\right].$$

The initial conditions ($k = 0$) of these sensitivity equations are

$$\frac{\partial X_i(0)}{\partial f_2} = \frac{\partial X_i(0)}{\partial \phi_2} = \frac{\partial Y(0)}{\partial f_2} = \frac{\partial Y(0)}{\partial \phi_2} = 0.$$

These equations must be solved simultaneously with the model equations letting $k = 1$, then $k = 2$, etc.

The partial derivatives of the constraint functions are

$$\frac{\partial h_1}{\partial f_2} = 1, \quad \frac{\partial h_2}{\partial f_2} = 0, \quad \frac{\partial h_3}{\partial f_2} = \phi_2\rho - 1,$$

$$\frac{\partial h_1}{\partial \phi_2} = 0, \quad \frac{\partial h_2}{\partial \phi_2} = -1, \quad \frac{\partial h_3}{\partial \phi_2} = 1 - (1 - f_2)\max_{1 \le k \le n}[\rho]. \qquad 1 \le k \le n.$$

The partial derivatives of all the parameters with respect to the independent parameters are

$$\frac{\partial f_2}{\partial f_2} = \frac{\partial \phi_2}{\partial \phi_2} = 1, \quad \frac{\partial \phi_2}{\partial f_2} = \frac{\partial f_2}{\partial \phi_2} = \frac{\partial f_3}{\partial \phi_2} = 0, \quad \frac{\partial f_3}{\partial f_2} = -1,$$

$$\frac{\partial \phi_3}{\partial f_2} = \phi_2[1 - \phi_2]/[\phi_2 - f_2]^2, \quad \frac{\partial \phi_3}{\partial \phi_2} = -f_2[1 - f_2]/[\phi_2 - f_2]^2.$$

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