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Research Article

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An Efficient Optimization Technique for Recovering Ventilation-Perfusion Distributions from Inert Gas Data

EFFECTS OF RANDOM EXPERIMENTAL ERROR

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ABSTRACT A variable metric optimization method of numerical analysis has been used to recover known distributions of intrapulmonary ventilation-perfusion ratios from inert gas data. Hypothetical lungs were simulated and corresponding inert gas retentions calculated. By using error-free retentions for seven gases and a 50-compartment model, it was possible to recover distributions containing up to three modes accurately and with greater efficiency than with other numerical methods. When random error of a magnitude consistent with present analytical techniques was introduced into retention data, the recovered distributions differed qualitatively from the original ones. This resulted from the ill-conditioned nature of the mathematical problem, which makes a recovered distribution extremely sensitive to small errors in retention. Thus, present levels of measurement error represent an important limitation in current techniques for deriving distributions from inert gas measurements.

INTRODUCTION

Efforts to define the intrapulmonary distribution of ventilation-perfusion ratios are of great interest because of the pivotal role of ventilation-perfusion mismatching in most abnormalities of oxygen and carbon dioxide exchange. Potential advantages of measurements of inert gas retention and excretion have been pointed out by Farhi (1) and experimental studies leading to equivalent two- or three-compartment models of the lungs have been reported by several groups. Recently there has been considerable interest in the technique developed by Wagner, Saltzman, and West (2) for deriving essentially continuous distributions of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$'s) from measurements of steady-state retention and excretion of a small number of inert gases of known solubility infused intravenously. The lung is considered as a model having a large number of compartments with specified $\dot{V}_A/\dot{Q}$'s equally spaced on a logarithmic scale. An iterative gradient method of numerical analysis is used to derive the fractions of total flow (or ventilation) for the compartments which are most compatible with the experimental measurements of retention (or excretion) in a least-squares sense. An important element of the analysis is the incorporation of the physiological constraint that compartmental flow (or ventilation) fraction can never be negative. The number of iterations employed varies from 400 to 4,000 and measurement errors are said to give rise to little inac-

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curacy, both when the distribution of $\dot{V}_A/\dot{Q}$ ratios is normal and abnormal.

The present study was intended (*a*) to investigate forms of numerical analysis which might be more efficient than the constrained gradient method and (*b*) to analyze in more detail the effect of unavoidable experimental error in the measurement of retention on the recovery of known distributions of flow fraction (f) vs. $\dot{V}_A/\dot{Q}$. The findings with the more efficient techniques indicate that qualitatively incorrect distributions are recovered frequently when error is present, and that current levels of measurement error are an important limitation of the inert gas technique as thus far used.

METHODS

By using the equation system developed by Farhi (1), steady-state retentions of seven inert gases were calculated for assumed unimodal, bimodal, and trimodal distributions of f vs. $\dot{V}_A/\dot{Q}$, with a 50-compartment model and $\dot{V}_A/\dot{Q}$'s ranging from 0.001 and 100 and spaced equally on a logarithmic scale. Blood-gas partition coefficients were chosen to cover the range of solubilities currently used experimentally (0.0060, 0.0405, 0.1110, 0.5800, 1.540, 2.490, and 12.48) and corresponded to the gases sulfur hexafluoride, methane, ethane, cyclopropane, fluroxene, halothane, and diethyl ether. Optimization methods of numerical analysis (3) were used to evaluate the effectiveness with which the original distributions could be recovered from the calculated retentions, both with and without randomly generated error in the values for retention. The mathematical approach was to iterate to the best least-squares fit for the following equation system, subject to the physiological constraint that values of flow in all compartments have to be greater than or equal to zero:

$$SSQ = \sum_{i=1}^{7}\left[R_i - \sum_{j=1}^{50}\frac{\lambda_i}{\lambda_i + (\dot{V}_A/\dot{Q})_j} f_j\right]^2 + \left[\sum_{j=1}^{50} f_j - 1\right]^2$$

where

SSQ = sum of squares
R_i = fractional retention of inert gas i for a lung containing j compartments
λ_i = blood-gas partition coefficient at 37°C of inert gas i
$(\dot{V}_A/\dot{Q})_j$ = ventilation-perfusion ratio of compartment j
f_j = fraction of cardiac output to compartment j

This equation is identical to that used by Wagner et al. (2) although, in their program, the last term on the right is generated by assuming a retention of 1.00 for an additional gas having a blood-gas partition coefficient of ∞. Our initial investigations used constrained optimization methods to incorporate the physiological constraint of positive flow, e.g., the method of feasible directions and a penalty function method (3). However, we subsequently realized that the constraint could be handled more effectively by a simple dummy variable substitution, y_j^2 for f_j, in the original equation system. This substitution allows the use of unconstrained optimization methods which are generally agreed to be more efficient for problems of this type. Since partial derivatives of the substituted equation are available, the unconstrained minimization can be carried out with a gradient method, a Newton-Raphson method, or a so-called "variable metric" or "Davidon-Fletcher-Powell" method (4, 5). For regular functions, all three methods work quite well. However, the function being evaluated has significant eccentricity and gradient methods frequently have an extremely slow rate of convergence, i.e., the solution changes perceptibly only over thousands of iterations. Because the original equation system becomes quartic rather than quadratic after the substitution of y_j^2 for f_j, the calculations required by Newton-Raphson methods are complex and time-consuming. The variable metric technique is a first-order method in which the sequence of iterates converges quadratically to a minimum and has good stability for highly eccentric functions. This technique was found to be most suitable for the present studies. On the basis of trials with a variety of distributions, a minimum value of SSQ was considered to have been reached when SSQ changed by $< 10^{-14}$ on successive iterations.

RESULTS

Fig. 1 illustrates the effectiveness of the variable metric method for recovering (*a*) unimodal, (*b*) unimodal with right-to-left shunt, (*c*) bimodal, and (*d*) trimodal distributions of f vs. $\dot{V}_A/\dot{Q}$ from error-free values of retention. The findings are typical of 20 similar distributions studied in detail. The relative efficiencies of the variable metric and gradient methods are illustrated by the fact that the gradient method required more than eight times as much computer time to achieve the same SSQ for the solution illustrated in panel (*c*).

Fig. 2 illustrates the effects of random experimental error on the recovery of a known unimodal distribution with a relatively small variance (mean $\dot{V}_A/\dot{Q} = 0.75$, log SD = 0.7). The inset shows (*a*) an error-free retention-λ curve for the known distribution and (*b*) seven points which differ slightly from the curve because of random error of 2–4% in the measurement of retention. The points were obtained by assuming that the experimental error involved in the determination of each retention is normally distributed with a mean of zero and SD's of ±6% for the lowest solubility gas and ±2.5% for other gases. These SD's were chosen to match the analytical reproducibility of currently available chromatographic measurements (6). The main portion of Fig. 2 shows the original f vs. $\dot{V}_A/\dot{Q}$ distribution and the flow fractions recovered from seven error-free and seven error-containing values of retention. The distribution recovered from error-free values of retention coincides essentially exactly with the true distribution. The distribution recovered from the values of retention containing the small random error (dashed line) differs qualitatively from the original distribution, being bimodal rather than unimodal over a two-decade range of $\dot{V}_A/\dot{Q}$. When 25 successive sets of data including random error of the same magnitude were generated for the same original distribution, a unimodal distribution

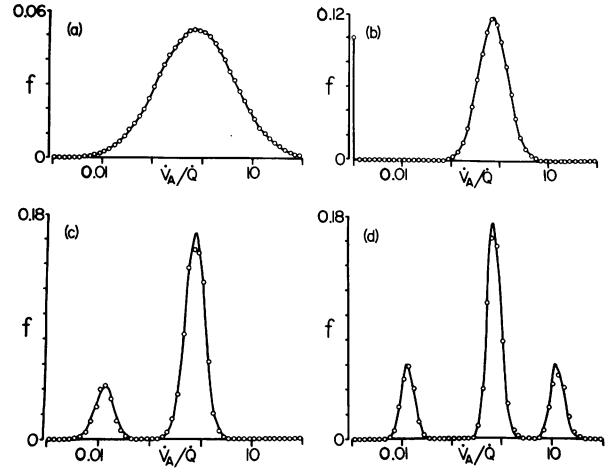

FIGURE 1 Recovery of known distributions of f vs. $\dot{V}_A/\dot{Q}$ from error-free data. The original distributions are shown by solid lines and the recovered distributions by open circles. Residual SSQ's varied from 10^{-7} to 10^{-18}. The recovered model and original distributions agree closely in each case. In additional studies, it was demonstrated that this agreement was independent of the particular values specified for $\dot{V}_A/\dot{Q}$ in the model.

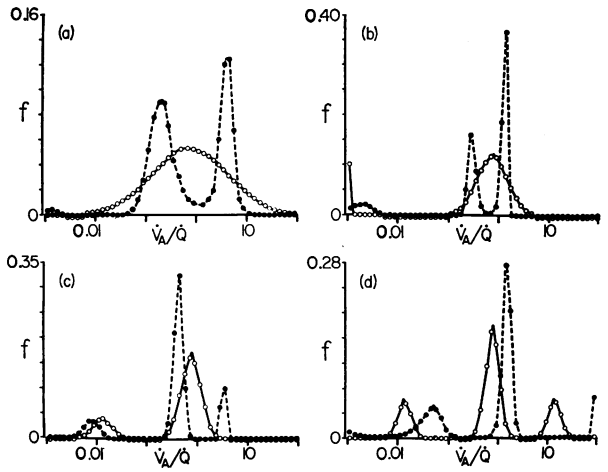

FIGURE 3 Recovery of the same four distributions illustrated in Fig. 1 in the presence of random error in the measurement of retention. Original distributions and those recovered from error-free values of retention are shown by solid lines and open circles, as in Fig. 1. Distributions recovered from the error-containing data are shown by solid circles and dashed lines and differ qualitatively from the original ones. Residual SSQ's for these distributions varied between 10^{-4} and 10^{-5}.

was recovered only twice. 19 of the remaining 23 distributions were bimodal and four trimodal. Fig. 3 illustrates the effect of random error of the same magnitude on (*a*) a unimodal log normal distribution with a larger variance, (*b*) a unimodal log normal distribution with a 10% right-to-left shunt, (*c*) a bimodal distribution, and (*d*) a trimodal distribution.

Fig. 4 illustrates that small random error has essentially the same effect on distributions recovered with the contrained gradient method developed by Wagner et al. (2). The original distribution is again unimodal log normal with a mean $\dot{V}_A/\dot{Q}$ of 0.75 and a log SD of 0.7. The bimodal distribution recovered with the variable metric method in the presence of small random error is the same as illustrated in Fig. 2; the residual sum of squares is 2.05×10^{-4}. The remaining three lines represent distributions recovered from the same set of error-containing data when analyzed with the constrained gradient method. When the analysis was terminated arbitrarily at 2,000 iterations, the recovered distribution appeared to correspond well with the original. However,

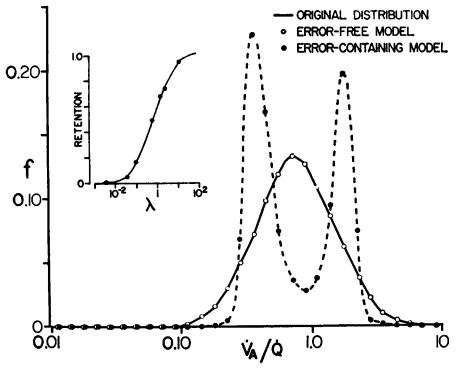

FIGURE 2 Recovery of a unimodal log normal distribution in the presence and absence of random error in the measurement of retention. See text for details. For clarity, only three of the five decades of $\dot{V}_A/\dot{Q}$ included in the model are shown. Both recovered distributions corresponded closely with the original one in the decades just above and below those illustrated.

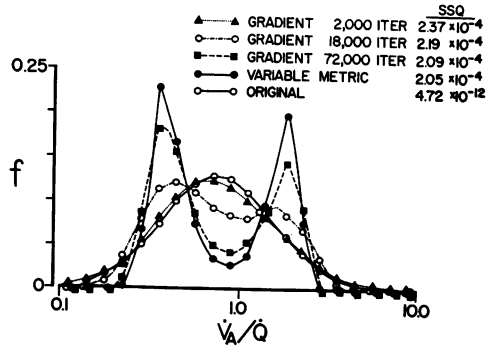

FIGURE 4 Comparison of variable metric and constrained gradient method for recovering the distribution illustrated in Fig. 2 from error-containing data. See text for details. Iter, iterations; SSQ, residual sum of squares.

TABLE I

*Comparison of Values of Retention Calculated Directly for Pairs of Distributions Illustrated in Figs. 2 and 3**

Inert gas λ	Fig. 2		Fig. 3a		Fig. 3b		Fig. 3c		Fig. 3d	
	R_1	R_2	R_1	R_2	R_1	R_2	R_1	R_2	R_1	R_2
0.0060	0.0101	0.0102	0.0277	0.0286	0.0926	0.0837	0.0704	0.0758	0.0677	0.0642
0.0405	0.0626	0.0638	0.1180	0.1144	0.1528	0.1526	0.1931	0.1872	0.1821	0.1793
0.1110	0.1487	0.1528	0.2174	0.2228	0.2321	0.2341	0.2867	0.2878	0.2593	0.2666
0.5800	0.4425	0.4511	0.4589	0.4716	0.4976	0.4967	0.5462	0.5647	0.4665	0.4568
1.540	0.6566	0.6621	0.6179	0.6207	0.6906	0.6905	0.7305	0.7315	0.6209	0.6119
2.490	0.7476	0.7520	0.6906	0.6916	0.7726	0.7751	0.8064	0.7975	0.6896	0.6885
12.48	0.9311	0.9357	0.8755	0.8872	0.9379	0.9468	0.9506	0.9382	0.8611	0.8665

* These values were obtained by considering each distribution to represent a 50-compartment lung with V_A/Q's equally spaced on a logarithmic scale from 0.001 to 100. R_1 = retention calculated directly for distribution shown by solid line; R_2 = retention calculated directly for distribution shown by dashed line. Corresponding values of R_1 and R_2 agree within ±3% in 32 of the 35 sets of retentions shown.

since the residual SSQ was greater than with the variable metric analysis, 2.37 vs. 2.05×10^{-4}, this distribution was not the best one mathematically. After 18,000 iterations the distribution was becoming bimodal. When the gradient analysis was carried out through 72,000 iterations, the distribution was clearly bimodal and the residual sum of squares approached that obtained with the variable metric method more closely, 2.09 vs. 2.05×10^{-4}. The 72,000-iteration gradient solution required nine times as much computer time as the variable metric solution.

DISCUSSION

This study confirms the report from Wagner et al. (2) that essentially continuous distributions of f vs. $\dot{V}_A/\dot{Q}$ containing up to three modes can be recovered from seven inert gas retentions if error-free values of retention and solubility are available. The use of the variable metric method of unconstrained optimization seems advantageous from the viewpoint of converging efficiently on the best least-squares solution. The study also indicates, however, that random experimental error can have profound effects on the recovery of distributions regardless of the form of numerical analysis employed. Figs. 2 and 3 illustrate the types of distributions recovered routinely in the presence of error of the magnitude achievable with current analytical techniques. The differences between the original and recovered distributions suggest a need for caution in interpreting detailed distributions calculated from presently available data. It should be noted that the solutions presented here, like those of Wagner et al. (2), have been obtained numerically and hence represent only an approximation to the best least-squares solution. It is possible that with greater computer accuracy and/or improved algorithms, solutions obtained in the presence of error might differ even more from the true solution.

As mentioned above, Wagner et al. (2) concluded that experimental error had little effect on their solutions. They presented results only for unimodal distributions, for which retention values do not appear to have been perturbed randomly. Our Fig. 4 indicates that reasonable agreement for a unimodal distribution can be obtained with the constrained gradient method if the solution is terminated sufficiently early. However, for an unknown distribution, it is not clear how to determine the appropriate termination point. Further, for bimodal and trimodal distributions, our experience indicates that the constrained gradient method, like the variable metric method, produces qualitatively incorrect distributions regardless of termination point.

It is also of interest that values of arterial P_{O_2} and P_{CO_2} calculated for original and recovered distributions did not usually reflect the different shapes of the distributions when error was present. For example, in 15 of the 25 successive trials including random error for the distribution illustrated in Fig. 2, values for arterial P_{O_2} and P_{CO_2} calculated for the recovered distribution were within ±3 mm Hg of the values calculated for the original distribution. Calculated values for arterial P_{O_2} and P_{CO_2} also agreed within ±3 mm Hg for the pairs of distributions illustrated in Figs. 3*a, b,* and *c*. Thus, we doubt that agreement of in vivo P_{O_2} and P_{CO_2} with values calculated from a recovered distribution is a useful test for verifying the detailed shape of the distribution.

It is likely that the difficulties arising from experimental error would be minimized if it were feasible to reduce the magnitude of the error appreciably. For example, when the original distribution in Fig. 2 was perturbed 25 succesive times with random error reduced in magnitude by a factor of five, a unimodal distribution was recovered in every case and all distributions corresponded closely with the original one. Similarly, bimodal distributions were always recovered when the

original bimodal distribution in Fig. 3*c* was perturbed ten successive times with random error also reduced in magnitude by a factor of five.[1] Possible approaches for achieving a fivefold reduction in error might include: (*a*) development of more precise analytical techniques; (*b*) multiple analyses of individual blood samples; (*c*) averaging retentions obtained from multiple samples in an individual patient, or single samples in a well-defined patient group. The practicality of any of these approaches is an open question. Since $SEM = SD/\sqrt{n}$, a fivefold reduction in error with existing techniques would presumably require averaging of 25 individual values. In repeated studies in individuals, or in large numbers of studies in specific groups, consideration would also have to be given to biological variation.

The effects of random error reflect the fact that qualitatively different $\dot{V}_A/\dot{Q}$ distributions can have values for inert gas retentions which are nearly identical. This can be illustrated by considering each of the distributions in Figs. 2 and 3 as representing a hypothetical lung and calculating absolute values of retention directly. Table I lists these values for the five pairs of distributions illustrated. The differences in shape of each pair of distributions correspond to differences in gas retention of only a few percent of absolute values. Thus, the recovery of distributions from retention-λ data is basically an ill-conditioned mathematical problem. This circumstance seems to be a fundamental limitation of the inert gas technique and will probably require detailed consideration in further attempts to derive unknown distributions from inert gas data.

[1] A preliminary publication (1974 *Fed. Proc.* **33**: 439) using constrained optimization techniques and indicating good agreement between known distributions and those recovered from data containing random error involved trials where the magnitude of error was only a few tenths of a percent.

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