Regional Ventilatory Clearance by Xenon Scintigraphy: A Critical Evaluation of Two Estimation Procedures

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Estimates of ventilatory clearance are usually made by inspecting xenon washout images. Quantitative computer procedures have been described that produce regional clearance rates, yet their accuracy is not well established. We define a mathematical model for scintigraphic ventilation data based on 96 clinical studies, and with this model we test the accuracy of two procedures used to estimate ventilatory clearance. The least-squares curve-fitting technique for both washin and washout data has the same accuracy as a modified Stewart-Hamilton method (A/H) that uses washout data alone. Both procedures demonstrate relative errors of less than 5% and coefficients of variation of 10–20% when regions with equilibrium count rates of 3 cps and clearance times between 10 and 90 sec are examined. Because the A/H procedure is preferred for its simplicity and speed, we analyze two of its main sources of error: early washin/washout termination and background activity. To measure regional ventilation by the A/H procedure, we recommend: (a) washin and washout periods at least three times the largest clearance time of clinical interest; b) a regional equilibrium count rate of at least 3 cps; and c) a 25- to 50-sec average of the equilibrium count rate.

J Nucl Med 20: 703–710, 1979

Scintigraphic studies with xenon isotopes are widely used clinically to evaluate regional ventilation. Xenon clearance or "washout" images reveal sites of abnormal pulmonary compliance or airway resistance (*1–3*). Hence, they provide functional data unavailable from roentgenographic studies. They also show greater regional sensitivity than can be achieved by standard pulmonary function tests or differential bronchospirometry (*4–6*). Regional ventilation is usually evaluated by inspecting washout images, but variation in regional lung volume and image intensity can reduce the accuracy of visual interpretation. Thus, quantitation is required to stage properly the degree of ventilatory dysfunction, to evaluate the response to therapy, and to assess ventilation-perfusion relationships. To this end, computers are used to generate "functional" images showing the distribution and magnitude of xenon clearance (*7–13*). Clearance rate constants are extracted from regional xenon activity curves by procedures based on simple models of pulmonary ventilation. Although little information is available on the reliability of these procedures, it is clear that their results depend on the count rate and on the appropriateness of the model chosen to represent lung function. Fortunately it is possible to use statistical techniques to measure the accuracy and precision of procedure results relative to a given model. The model may be used to define the

Received Nov. 2, 1978; revision accepted Feb. 14, 1979.

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methods of data collection that will provide optimal results.

We propose a simple model that is consistent with the characteristics of scintigraphic ventilation studies. We use this model to test two common analytical procedures and to investigate two sources of error that affect the preferred procedure.

MATERIALS AND METHODS

Patient studies. In order to estimate ranges of clinically observed count rates and clearance times, we reviewed ventilation-perfusion scintigrams of 96 patients. Thirty-two studies were performed to confirm the diagnosis of pulmonary embolism, 45 for evaluation of fibrotic lung disease, and 19 for assessment of obstructive lung disease. All ventilation studies were performed during tidal breathing. The patient, seated with back to gamma camera, breathed from a closed-loop spirometer system containing 15–20 mCi of xenon initially and 2 mCi/liter when equilibrium with the patient's airspace was reached. Sequential images were obtained during 5–6 min of washin, and 5–6 min of washout. All scintigraphic data were recorded in list mode on magnetic tape, so that serial 64- by 64-pixel images, with 5-sec collection times, could be produced by minicomputer processing. The time-activity curve of the full lung, or of any number of pixels, could be examined by the selection of an appropriate "area of interest" (Fig. 1). Typical count rates in a single pixel ranged from 10 to 25 counts/5 sec, depending on the portion of the lung examined. Images of air-space volume, regional perfusion, clearance time constant, and ventilation (Fig. 2) were produced to supplement the interpretation of the routine camera images. Within this patient group, more than 75% of regional clearance times fell between 10 and 100 sec.

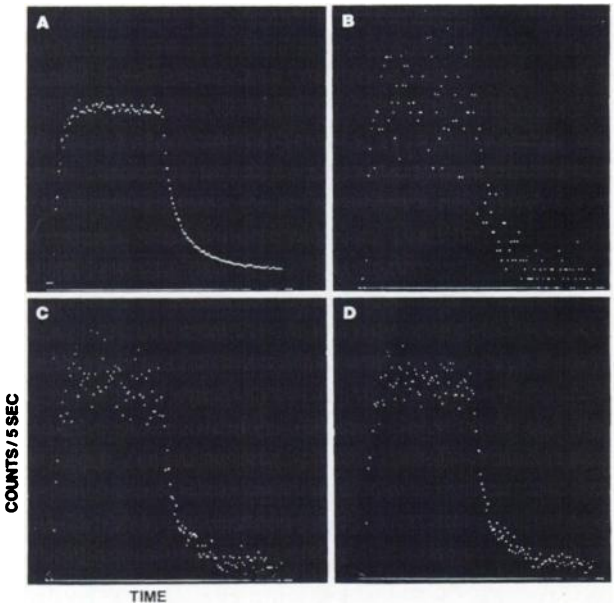

FIG. 1. Xenon time-activity curves during ventilation study. Each curve point represents a 5-sec count sum. Curves are scaled to demonstrate reduction in Poisson noise with increasing region size. (A) Full lung activity curve. (B) Single-pixel activity curve containing 15 counts per interval during equilibrium. (C) Four-pixel curve. (D) Nine-pixel curve. Failure to return to pre-study baseline is attributed to activity in "background" structures.

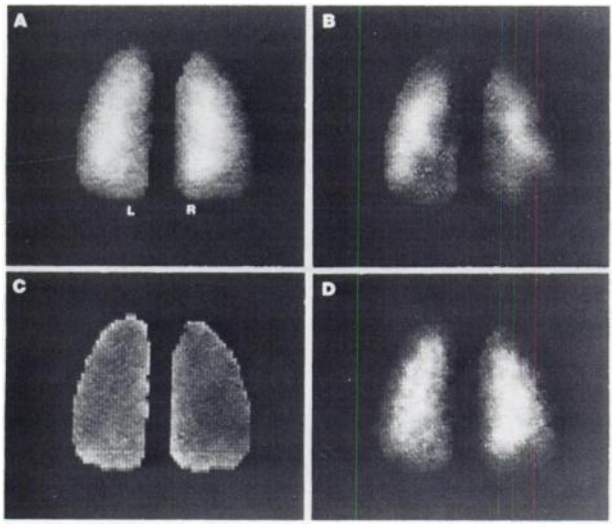

FIG. 2. Computer-processed images of posterior lung fields. (A) Regional volume, obtained from equilibrium portion of ventilation study. Regional intensity is proportional to regional lung volume. (B) Perfusion by Tc-99m macro-aggregated albumin. (C) Clearance time by Stewart-Hamilton modification (A/H). Intensity is proportional to time. Note increasing clearance times near lower lung margins. (D) Regional ventilation obtained by dividing regional volume by regional clearance time. Comparison with perfusion image indicates region of high ventilation-to-perfusion ratio in right lower lung field.

Mathematical model of ventilatory function. We represent the lung by a large collection of independent compartments each characterized by a volume and a time constant for tracer clearance. This is a minimal model, which retains sensitivity to regional lung dysfunction and also fits the main features of the scintigraphic data. To correspond to limitations imposed by the imaging procedure, and to avoid distracting complexities, we assume the following additional conditions:

1. The time constant of each compartment does not change during the procedure.

2. Each image pixel is associated with a single compartment. We ignore inhomogeneities of ventilatory function both perpendicular to the plane of the scintigraphic image and within a single pixel. Any uncertainty related to lung motion is neglected.

3. Each compartment exchanges gas with an external environment that contains a fixed level of xenon during washin and no xenon during washout.

4. Redistribution of xenon from the lung into other "background" portions of the body is neglected. The washin and washout phases [WI(t), WO(t)] of a scintigraphic study, illustrated in Fig. 3A, are described by a mathematical model that incorporates these assumptions and describes the dynamics of the count rate in a single pixel:

$$WI(t) = N_{eq}(1 - e^{-t/\tau}), \text{ and} \quad (1)$$

$$WO(t) = N_{eq}(1 - e^{-T/\tau})e^{-(t-T)/\tau} \text{ for } t \geq T, \quad (2)$$

where T is the duration of washin, N_{eq} is the equilibrium count rate, and τ is the time constant. Our goal is to determine τ, which characterizes the ventilatory clearance time. This is equivalent to the average clearance time of the xenon in the compartment, or 1.44 times the biologic half-life of the gas within that compartment.

Clearance-time estimation procedures. In a recent review (*3*), Secker-Walker cites the commonly used methods for determining ventilatory clearance constants:

1. curve-fitting to washout;
2. the Stewart-Hamilton equation; and
3. linear plot of washout on semilogarithmic coordinates.

We have also considered:

4. the two-area technique (*16*); and
5. the three-area technique (*16*).

Because errors introduced in the smaller numbers are magnified by a logarithmic transformation, the semilogarithmic plotting method, although convenient for hand work, has little to recommend it when a computer is available. Our unpublished simulation studies have shown that both the two-area and three-area techniques are inferior to any of the others for dealing with pulmonary scintigraphic data. Therefore, only curve-fitting methods and the Stewart-Hamilton equation remain for serious consideration.

Curve-fitting by least squares. The clearance time constant may be determined by performing a least-squares fit of a model to the scintigraphic data. The proper model for fitting is the definite integral of Equations 1 and 2 over successive intervals Δt (Fig. 3B), and is stated analytically as

$$WI(i) = N_{eq}[\Delta t - \tau(e^{-i\Delta t/\tau} - e^{-(i+1)\Delta t/\tau})] \quad (3)$$

for washin, and

$$WO(i) = N_{eq}\tau(1 - e^{-T/\tau})(e^{-i\Delta t/\tau} - e^{-(i+1)\Delta t/\tau}) \quad (4)$$

for washout, where i is the sequential number of the interval of length Δt during washin or washout.

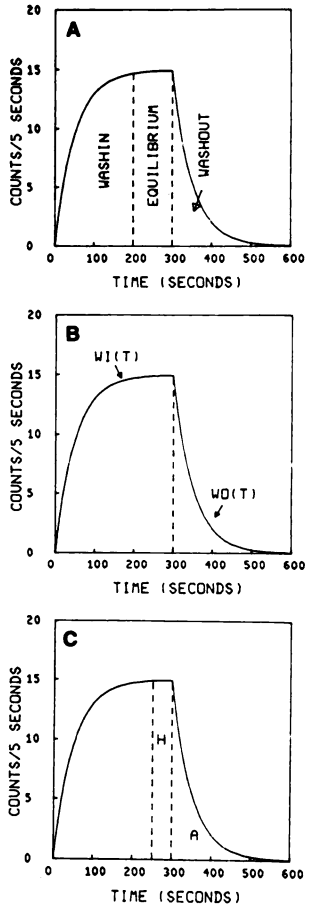

FIG. 3. (A) Idealization of xenon level in a single compartment, showing the washin, equilibrium and washout phases. During washin, xenon concentration in inspired air is constant, and during washout no xenon is inspired. Tracer in compartment is constant during equilibrium. (B) Method of least squares. Curves WI(t) and WO(t) are least-squares models for single-compartment washin and washout processes Eqs. (3 and 4). (C) A/H method. The values of A and HΔt are obtained by summing counts in corresponding regions.

The summation of observed counts over the intervals is the equivalent of this definite integral. It is possible to restrict the study to washin or washout, or both may be combined. In all three cases we computed the parameters N_{eq} and τ using a modified Marquardt-Levenberg iterative curve-fitting procedure (*17*).

Stewart-Hamilton equation. This equation, as applied to the analysis of washout studies, is described in detail elsewhere (*18-19*). As suggested by others (*14*), we define H as the total counts during an equilibrium interval, ΔT, in order to reduce its coefficient of variation, and A as the total number of counts during washout (Fig. 3C). Thus, $H = N_{eq}\Delta T$, $A = N_{eq}\tau$, and $\tau = A\Delta T/H$. When two compartments with different τ values are combined in the same pixel, the resulting estimate, $\hat{\tau}_C$, is sim-

ply the arithmetic mean of the values of τ in the two compartments. If one compartment is larger in volume than the other, then the value of $\hat{\tau}_C$ is the volume-weighted mean of the values in each compartment. The use of the Stewart-Hamilton equation requires a) that the washin process reach equilibrium, and b) that washout be taken to infinite time. Subsequently we shall refer to this modified approach as the A/H procedure.

Computer simulation of scintigraphic ventilation data. Twenty noise-free washin/washout curves were generated according to the scintigraphic model (Equations 3 and 4) for each of nine values of τ (10–90 sec in steps of 10 sec). The curves were constructed with 300-sec (T) washin and washout periods and constrained to an equilibrium count level (N_{eq}) of 15 counts per 5-sec interval (Δt). Random count fluctuations were superimposed on each curve point by a Poisson noise generator. The A/H and the least-squares procedures were applied to each curve to obtain an estimate for τ ($\hat{\tau}$). The percentage error of the mean $\hat{\tau}$ for the 20 curves, relative to the actual value of τ, was used to measure procedure accuracy. Precision was estimated from the coefficient of variation (standard deviation/mean) of $\hat{\tau}$ over the 20 curves produced for each known τ. With 20 simulations, the mean and coefficient of variation were estimated to within 5%.

Asymptotic statistical analysis of the A/H procedure. In the presence of noise, the A/H calculation applies only to expected values, and a more complete statistical analysis is required to obtain asymptotic estimates of relative error and coefficients of variation. The analysis is set forth in the appendix to this paper.

Error sources. *Washin/washout data-collection time.* When the clearance time constant is sufficiently large that equilibration is not achieved by the end of washin, the conditions of the Stewart-Hamilton equation are not met, and the A/H formula produces biased estimates of τ. Using the asymptotic analysis (Appendix, Eq. A-9) we can compute the relative error in $\hat{\tau}$ for any choice of T and τ.

Background. During the washin and equilibrium phases of the ventilation study, xenon passes from the air space of the lung into the alveolar walls, the blood stream, and to other parts of the body. During washout, these compartments act as a source of tracer, returning xenon to the alveolar airspace. The presence of this "background" in a pixel curve is manifest as a failure of the count rate to return to the prestudy baseline. It is clear from inspection of the data (Fig. 1) that background exists, and represents a departure from the assumptions of the ventilation model. The background compartments not only return xenon to the airspace during washout, but they may also appear with the lung in the image and contribute directly to the number of counts observed. A physical model incorporating these effects would be quite complex. As an approximation, we consider a constant background level and determine its effect on the A/H procedure.

With a background level of N_b and a given τ, expressions for A and H are $A_b = N_bT + N_{eq}\tau$ and $H_b = (N_b + N_{eq})\Delta T$. Defining τ_b as $A_b\Delta T/H_b$, we compute the effects of different constant-background count rates on the estimates of τ.

RESULTS

Curve-fitting methods. Using both washin and washout data, the method of least squares was apparently unbiased (Fig. 4A). For all values of τ, the average $\hat{\tau}$ for 20 simulations had less than a 5% relative error. The coefficient of variation (Fig. 4B) changed smoothly between 7% for large values of τ to around 20% for τ = 10 sec. When the fit was restricted to washin or washout data alone, however, the average relative error was sometimes greater than 5%, and the coefficient of variation approximately doubled, ranging from 15% to 43% for washin and 12% to 40% for washout as τ decreased from 90 to 10 sec.

Area/Height analysis. The A/H analysis was apparently unbiased (Fig. 4C); the average $\hat{\tau}$ for 20 simulations fell within 5% of the correct value for all values of τ but one. The asymptotic statistical estimate of the relative error (Fig. 4D, solid line) was slightly smaller than that obtained by the simulation. The coefficient of variation ranged from 9% for τ = 90 sec to 23% for τ = 10 sec. The asymptotic estimate of the coefficient of variation was in good agreement with the simulations.

Error sources. *Washin/washout data-collection time.* Figure 5 shows the predicted relative error of $\hat{\tau}$ over the range from 10 to 200 sec. The effect of increasing the duration of both the washin and washout data-collection time from 300 sec to 800 sec is also shown. As the data-collection time is increased, the assumptions of the Stewart-Hamilton equation are more nearly satisfied and the relative error decreases accordingly.

Background. The A/H method is very sensitive to the presence of background. Figure 6 shows the effect of adding a constant background of 1–5% of the equilibrium level to both A and H. For small values of τ and a 5% background, the relative error may be much larger than 100%. As is apparent from Fig. 1, the background may in fact be considerably larger than 5%.

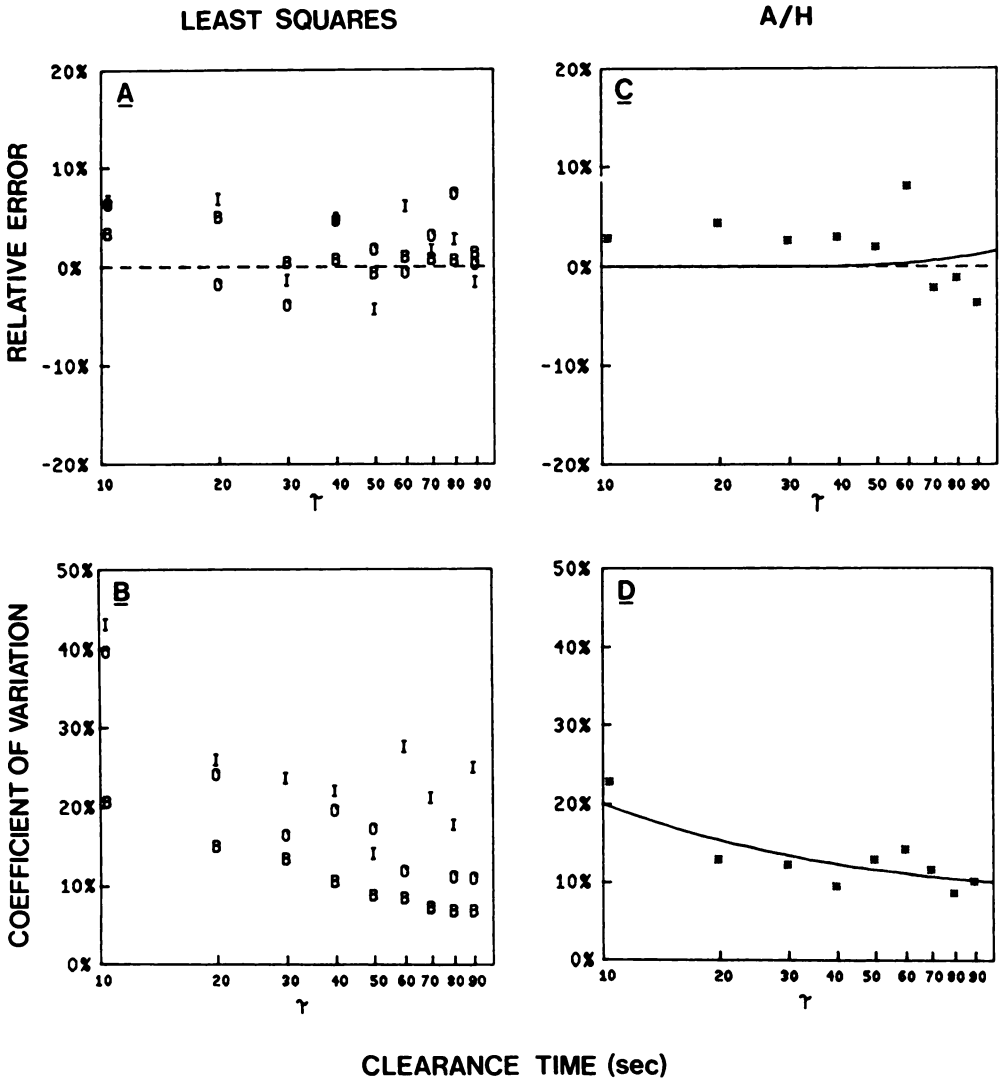

FIG. 4. Results of procedure reliability studies. (A) Relative error of $\hat{\tau}$ by curve fitting. When both washin and washout data are used, bias is less than 5% at all values of τ. (B) Coefficient of variation for τ determination by curve fitting. Symbols "i," "o," and "b" denote, respectively, washin alone, washout alone, and both washin and washout. When both portions of scintigraphic study can be used, coefficient of variation of τ varies between 10 and 20%. (C) Relative error of $\hat{\tau}$ by A/H. Square dots show computer-simulation results; solid line represents results of asymptotic statistical analysis. Dashed line is correct result. (D) Coefficient of variation for τ determination by A/H. Dots show simulation result, whereas solid line is result from asymptotic analysis.

DISCUSSION

Comparison of A/H and least-squares methods. Using both washin and washout data for least-squares curve fitting, the A/H and least-squares methods are essentially equivalent in accuracy and precision. Unfortunately, if washin data are not used, and only the washout data are fitted, the least-squares method is not as reliable as A/H. This distinction is important clinically, since most studies are performed with single-breath and/or closed-loop-spirometer xenon administration, neither of which satisfies the condition of constant xenon activity in the inspired air.

One important difference between the two methods is their cost. The time required to obtain a solution by the least-squares method depends critically on the initial estimate of τ. We chose the "correct" τ as the initial estimate, yet the method of least squares required significantly more computer time than the A/H method. Under clinical conditions, when the initial estimates are substantially in error, the least-squares method may take 20–50 times as much computer time. Thus, in clinical applications we prefer the A/H analysis for single-pixel data because of its greater reliability, simplicity, and speed.

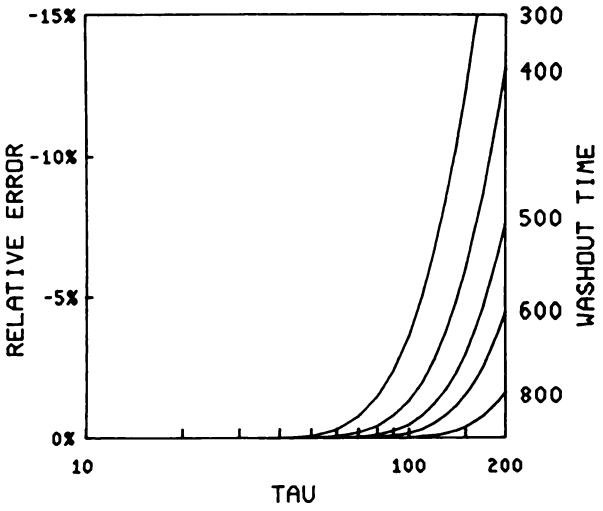

FIG. 5. Asymptotic prediction of relative error for τ in range 0–200 sec. There is negligible error in τ less than 100 sec when the washout period is greater than 300 sec. Curves show error reduction associated with lengthening of washout period from 300 to 800 sec. There is little improvement for values less than 100 sec.

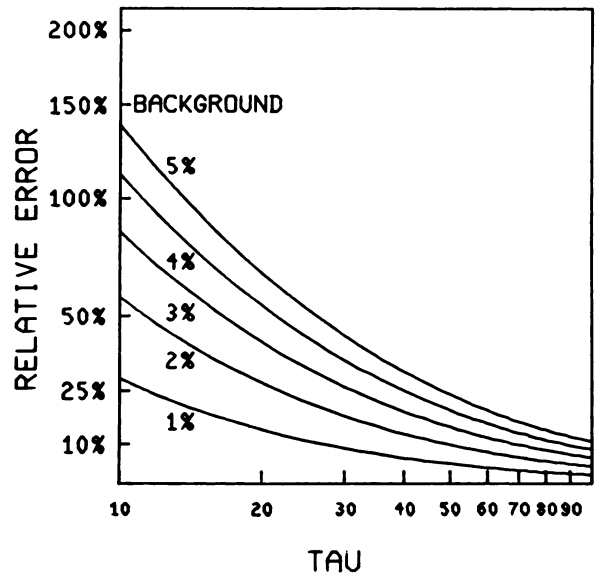

FIG. 6. Effect of constant background on relative error of A/H method. Curves show relative error caused by constant background of 1–5% of equilibrium rate. Error in τ is proportional to background magnitude and is strongly affected by magnitude of τ. A 5% background may cause a 100% error in estimate of small τ.

Optimization of study parameters. The ventilation study procedure can be altered either by changing the duration of washin and washout, or by changing the amount of tracer administered to the patient (equilibrium count rate). In order for the A/H method to have less than 5% relative error, it is necessary that the washout time (T) exceed τ by a factor of at least three. Thus, if the largest τ is 100 sec, a T of 300 sec is just sufficient.

The coefficient of variation improves in proportion to the square root of the increase in count rate. Our simulations were based on a level of 15 counts/5-sec interval; a fourfold increase in count rate, to 60 counts/5 sec, would halve the coefficient of variation. The equilibrium count rate per pixel may be increased without increasing dosage to the patient by reducing the resolution of the image. We used images containing 64 by 64 pixels, but a matrix of 32 by 32 pixels would increase the counts in a single pixel fourfold, and halve the coefficient of variation.

In performing an A/H analysis we are obliged to choose the duration of the equilibrium frame, ΔT. In the simulations we chose 50 sec. According to the asymptotic analysis, the reduction of ΔT to 25 sec reduces the relative error but increases the coefficient of variation. This reduction in the error was not apparent in our simulation, so we prefer a ΔT of 50 sec. Increasing ΔT beyond 50 sec for a fixed T of 300 sec increases the error, because regions with larger values of τ do not achieve equilibrium by the beginning of the ΔT period.

Error sources. *Washin/washout data-collection time.* In some regions of severely obstructed or poorly compliant lungs, clearance constants longer than 100 sec may be observed. The asymptotic analysis of the A/H procedure shows that estimation of τ becomes increasingly unreliable when the true τ is larger than 100 sec. In the absence of background, this difficulty may be overcome by increasing the duration of the ventilation study, as is shown in Fig. 5.

Respiratory motion. This has been neglected in the model, but it is clear that as the lungs vary in volume, they also vary in the amount of tracer they contain. Respiratory movement also causes pixels lying near the edge of the lung to receive counts from outside the lung during some phase of the respiratory cycle. Since the nonlung tissue clears tracer much more slowly than lung tissue, the value of τ for these pixels is increased. Although the effect is not extreme in pixels well within the lung, it appears prominently at the base and outer edges, as seen in the functional image of Fig. 2C. Because of this effect, τ functional images and images derived from them (ventilation, ventilation-perfusion ratios) should be interpreted with caution near the diaphragm.

Background. The model neglects the loss of xenon from the pulmonary air space into lung tissue and to the extrapulmonary compartments. This tissue will act as a source of tracer to the lung during washout and will be manifest as a failure of the

washout time-activity curve to return to the pre-study baseline. The problem of background is potentially the most serious, since τ values produced by the A/H method are very sensitive to its presence. To correct for background, a number of approaches have been suggested (*14,20*). The use of a global correction ignores the likely variation of background over the lung. The use of any regional correction is equivalent to the assumption of a model with more than two parameters. Our simulations show that parameters for such models are determined with very poor precision.

It is clear that the problems of background determination and correction are complex. Because improper background-correction procedures may introduce errors greater than those caused by background itself, it is evident that any correction procedure should be used with caution; those that have not been carefully investigated probably should not be used at all.

CONCLUSION

Clinically, scintigraphic estimates of τ reveal the effect of regional pulmonary resistance and compliance on ventilatory clearance time. With partial airway obstruction or loss of alveolar integrity, regional clearance time increases relative to normal areas. Thus, the ability to detect early ventilatory dysfunction and to follow its course under therapy will depend on the reliability of the method of τ quantitation.

Quantitative interpretation of scintigraphic data requires a physiologic model. The chosen model both specifies and qualifies the conclusions that can be drawn from it. We have used an explicitly stated model to define a data-collection procedure for ventilatory clearance studies, and to interpret the results obtained from those studies. We conclude:

1. The reliability of the least-squares fit of washin and washout data is comparable to the reliability of the A/H techniques on washout data alone. The A/H technique is preferred for clinical use because of its simplicity and speed.

2. To measure τ values reliably in the range of 10–100 sec, washin and washout study should last 300 sec. The equilibrium count rate should be averaged over the last 50 sec of washin time, and equilibrium count rates in image pixels should be at least 3 cps.

3. The main sources of error in τ estimation include early termination of washin and washout, respiratory motion, and the presence of background.

APPENDIX

We assume that the activity detected in a region of lung is a random variable with a Poisson distribution. Since the amount of xenon present during washout is time-dependent, the Poisson process will also be time-dependent, with a rate given in Eqs. 1 and 2. In the absence of counting uncertainties, given that equilibrium is achieved, it is easily shown that

$$\tau = \Delta T(N_2/N_1), \tag{A-1}$$

where N_1 is the total number of counts in the equilibrium interval $(T-\Delta T,T)$ and N_2 is the total number of counts during washout. Since sampling uncertainties do exist, Eq. A-1 can be used only to furnish a statistical estimate of τ, which we will denote by $\hat{\tau}$. We will be interested in the relative error and the coefficient of variation of $\hat{\tau}$, that is $E(\hat{\tau})/\tau$ and $\sigma(\hat{\tau})/E(\hat{\tau})$, and their relation to the adjustable parameters T and ΔT. Since N(t) in Eqs. 1 and 2 is the rate parameter of a Poisson process, it follows that the cumulative counts,

$$N_1 = \int_{T-\Delta T}^{T} N(t)dt,$$

and

$$N_2 = \int_{T}^{\infty} N(t)dt, \tag{A-2}$$

also have a Poisson distribution with average values

$$\mu_1 = E(N_1) = N_{eq}\tau\left(\frac{\Delta T}{\tau} - 1 + e^{-\Delta T/\tau}\right),$$

and

$$\mu_2 = E(N_2) = N_{eq}\tau\left(\frac{T-\Delta T}{\tau} - e^{\Delta T/\tau} + e^{-T/\tau}\right). \tag{A-3}$$

The bias and variance of $\hat{\tau}$ are given by

$$E(\hat{\tau}) = \Delta T\, E(N_2)\, E(1/N_1)$$

and

$$\sigma^2(\hat{\tau}) = (\Delta T)^2 \{\sigma^2(N_2)E(1/N_1^2) + \sigma^2(1/N_1)E^2(N_2)\}, \tag{A-4}$$

since N_2 and $1/N_1$ are independent random variables. Some caution is required in the evaluation of $E(1/N_1)$ and $E(1/N_1^2)$, since the probability that $N_1 = 0$ is finite. However, we shall exclude this difficulty by conditioning on the probability that $N_1 \neq 0$, as is in fact done in practice. We therefore have

$$E(N_1^{-r}) = (e^{\mu_1} - 1)^{-1} \sum_{n=1}^{\infty} \frac{\mu_1 r}{n! n^r}. \tag{A-5}$$

Given the typical parameters of a clinical study, μ_1 is greater than 30 for $\tau < 100$ sec, so that μ_1 can be considered large compared with one. We therefore need the asymptotic evaluation of Eq. A-5. To derive one we use the integral representations

$$n^{-1} = \int_0^{\mu_1} e^{-nt}dt,$$

and

$$n^{-2} = \int_0^{\infty} t\, e^{-nt}dt, \tag{A-6}$$

and perform the sums explicitly. In this way we find

$$E\left(\frac{1}{N_1}\right) = \frac{1}{e^{\mu_1}-1}\int_0^{\mu_1} \frac{e^v - 1}{v}\, dv$$

and

$$E\left(\frac{1}{N_1^2}\right) = \ln \mu_1 E\left(\frac{1}{N_1}\right) + \frac{1}{e^{\mu_1}-1}\int_0^{\mu_1} \ln v\left(\frac{e^v-1}{v}\right) dv. \quad \text{(A-7)}$$

From these expressions one can derive the asymptotic expansions

$$E\left(\frac{1}{N_1}\right) \approx \frac{1}{\mu_1} + \frac{1}{\mu_1^2} + \frac{2}{\mu_1^3} + \ldots \quad \text{(A-8)}$$

$$E\left(\frac{1}{N_1^2}\right) \approx \frac{1}{\mu_1^2} + \frac{3}{\mu_1^3} + \frac{11}{\mu_1^4} + \ldots$$

Since $(1/N_{eq}\tau)$ is a small parameter, we can use Eq. A-8 to derive the following expansion for the normalized expectation of $\hat{\tau}$:

$$\frac{E(\hat{\tau})}{\tau} = (1 - e^{-T/\tau})\left[1 - (e^{-T/\tau})\left(\frac{e^{\Delta T/\tau} - 1}{\Delta T/\tau}\right)\right]^{-1} + 0\left(\frac{1}{N_{eq}\tau}\right). \quad \text{(A-9)}$$

Generally, all terms but the first are negligible. To a good approximation we find the coefficient of variation to be:

$$C = \frac{\sigma(\hat{\tau})}{E(\hat{\tau})} = \left[\frac{1}{N_{eq}\Delta T}\left(1 + \frac{\Delta T}{\tau}\right)\right]^{1/2}. \quad \text{(A-10)}$$

ACKNOWLEDGMENTS

The authors thank James J. Bailey, Thomas B. Stibolt, Eugene K. Harris, and John E. Fletcher for helpful criticism and encouragement. We are also grateful to Joseph F. Wilson and Camille B. Vermess for processing the scintigraphic data, and to Elizabeth Fleetwood for preparation of the manuscript.

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