Indicator Transit Time Considered as a Gamma Variate

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■ Several theoretical formulations have recently been proposed to explain the shape of peripheral indicator dilution curves.[1-5] One such mathematical approach utilizes convolution integrals,[1, 3, 4, 6-11] in which concentration of the indicator is handled as an unknown and *unspecified function of time, C(t).* The widespread use of this method, however, will be limited because the required mathematical manipulations, when applied to curves obtained in vivo, involve intricate and lengthy calculations. This type of analysis would be facilitated if the indicator concentration could be conveniently expressed as a *specific function of time.*[9, 10] If such a suitable function were available, it would also be possible to characterize more accurately normal and abnormal indicator dilution curves and perhaps to gain insight into some of the factors determining the shape of the curves. In addition, the availability of such a function would allow more efficient processing of experimental curves by high-speed computers.

A number of theoretical and empirical mathematical expressions for $C(t)$ have been suggested.[2, 4, 5, 12, 13] These have found limited application and have not been subjected to extensive experimental verification using a large number of normal and abnormal curves. One expression for $C(t)$, proposed by Evans in 1959,[12] has a graphical representation which bears a remarkable resemblance to indicator dilution curves without recirculation (see Appendix). With only minor changes in notation, this function can be expressed in the form,

$$C(t) = K(t - AT)^{\alpha} e^{-(t-AT)/\beta} \qquad (1)$$

t = time after injection
$C(t)$ = indicator concentration at time, t
K = constant scale factor
AT = appearance time
α, β = arbitrary parameters

This expression for $C(t)$ has convenient mathematical properties and can be shown to be applicable to a wide variety of indicator dilution curves. In the present study curve-fitting techniques were used to find appropriate noninteger values of α and β (equation 1) for 114 normal and abnormal curves. Excellent fits were obtained for each of the curves. From these observations and from the known mathematical characteristics of the function in equation 1, it was found that indicator transit time exhibits essentially the same mathematical properties as do a number of random variables, known as "gamma" variates (see Discussion). The evaluation of equation 1 as a potentially useful means of describing indicator dilution curves forms the basis of this report.

Methods

Peripheral arterial dye dilution curves (indocyanine green), which had been obtained over a three-year period at the Duke Cardiovascular Laboratory from catheterized patients without shunts, were studied. A total of 114 curves were selected from 70 patients and 2 normal subjects. Of these curves, 109 were from patients with catheter-proven valvular heart disease, 3 were from patients proven at catheterization to be hemody-

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namically normal, and 2 were from normal subjects. The curves were obtained following the injection of indocyanine green dye into the right atrium or pulmonary artery, by continuously sampling peripheral arterial blood through a linear cuvette densitometer (Colson-Gilford). The resulting dilution curve was recorded by means of an Electronics for Medicine photographic recorder. All of the 114 curves were plotted on semilog paper and extrapolated in the standard Stewart-Hamilton manner.[14] Details of the technique as employed in this laboratory have been published previously.[15]

Many of the curves often had obvious "smearing," i.e., prolongation of the downslope, which has been ascribed to the elongation of the injected slug of dye as it passes through blood vessels and mixing chambers of various capacities.[5] If Shillingford's spread/appearance-time ratio[16] is used as an index of the degree of this smearing, the 114 curves included 48 curves which showed no or minimal smearing (S/AT ratio < 2.0), 43 showed mild to moderate smearing (ratio 2.0 to 3.0), and 23 showed marked smearing (ratio $>$ 3.0).

The ordinates of the extrapolated curves were measured at one-second intervals and entered on IBM punch cards. Also included as "input" on the

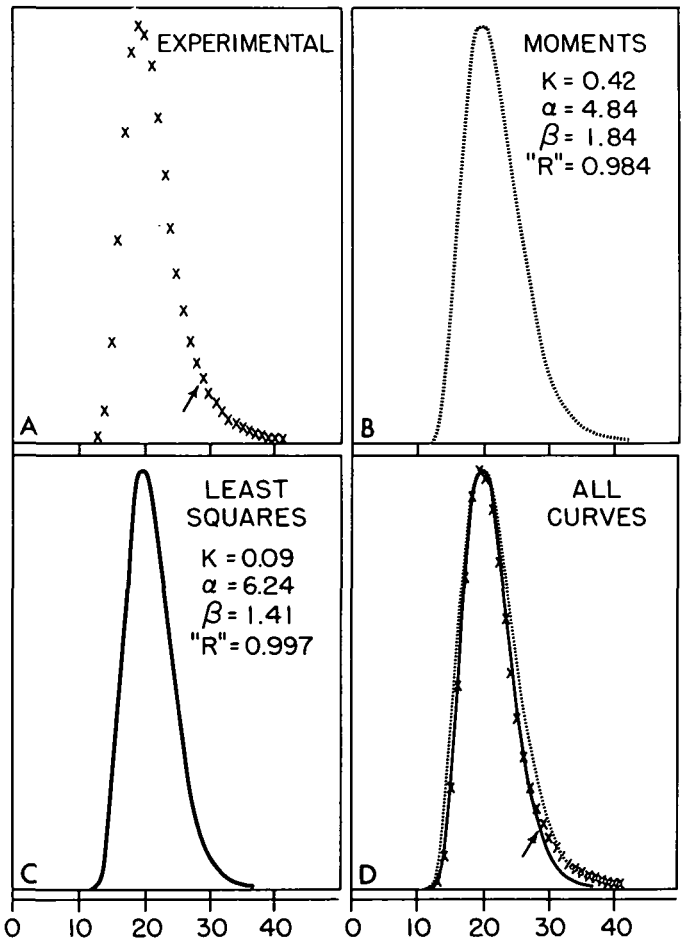

FIGURE 1

Comparison of a logarithmically-extrapolated experimental dye curve from a normal human subject (panel A) with theoretical curves fitted by moments (panel B) and least squares (panel C). In panel D, all three curves are superimposed on one another. The abscissa represents time (seconds) following dye injection, and the ordinate is a linear plot of dye concentration. Small arrows in panels A and D on the downslope of the curve indicate the point at which logarithmic extrapolation begins. Values of the parameters in equation 1, along with the intraclass correlation coefficients, "R," are indicated in panels B and C.

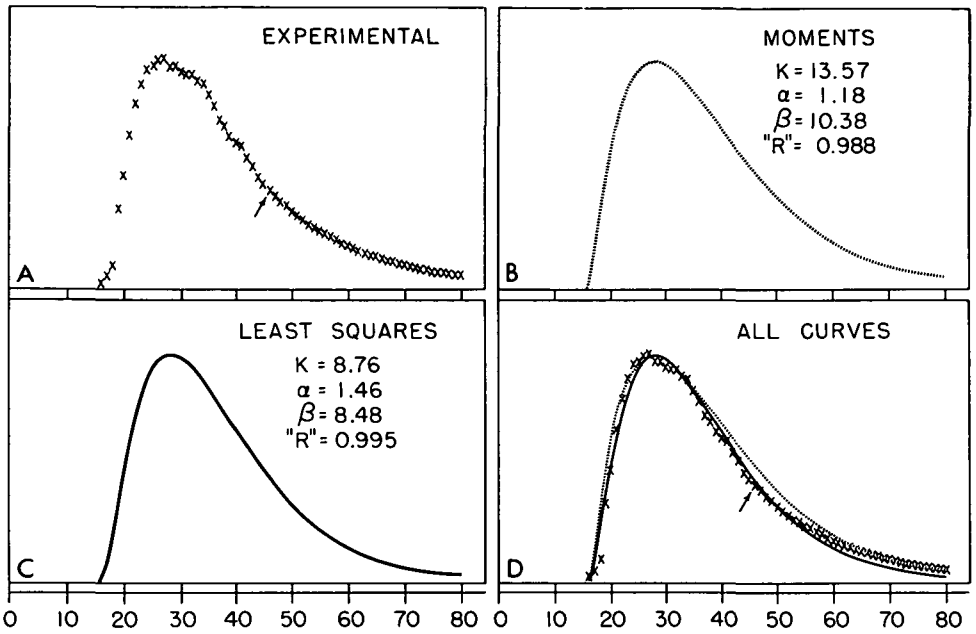

FIGURE 2

An abnormal dye curve, fitted by moments and least squares, from a 54-year-old female patient with mitral stenosis and pulmonary hypertension. Notation is the same as in figure 1.

punch cards for each curve were a) the time following injection (seconds) associated with the first ordinate from the observed curve, b) the observed appearance time (measured from the midpoint of the time required to complete the injection to the initial deflection of the curve), c) the calibration factor (to convert millimeters of deflection on the photographic record to mg per cent of indocyanine), and d) the volume of injected dye.

An IBM 7072/1401 digital computer was programmed to fit to the experimental curves a mathematical function of the form (1) above using each of two different mathematical approaches: a) the method of moments, b) the method of least squares. The application of the method of moments is described in the Appendix. The least squares fits were found by developing a program for the Gauss-Newton method of fitting nonlinear functions as modified by Hartley.[17, 18] The computer programs were designed to find the appropriate values of α and β by both methods and to provide plots of the original experimental data and the calculated curves.

From each of the 114 extrapolated curves the predicted and corresponding observed values at one-second intervals for indicator concentration were compared to each other. In order to provide a measure of the deviations from the line of identity, it was elected to compute "intraclass correlation coefficients" for each curve instead of the more familiar coefficients of linear correlation.[19] It is important to note that, when values of R are close to $+1$, as they were in this study, very slight increases in R represent important differences in closeness of fit.

To examine the possibility of applying the curve-fitting techniques directly to experimental curves without the necessity of logarithmic extrapolation, 22 curves were chosen for further study. These curves, as originally recorded with recirculation intact, were digitized at one-second intervals and the data entered on punch cards. The least squares method was applied to the first portion of these curves, from appearance time to a point midway in time between the first peak and the first minimum. The method of moments could not be employed, because the area under the extrapolated curve is required in the application of this method (see Appendix, equations 28 and 29). From each of the 22 nonextrapolated curves, an estimate of the cardiac output was obtained by dividing the integrated area under the fitted function into the amount of dye injected. To compare the cardiac output estimates derived in this fashion with the corresponding values obtained by the "classical" Stewart-Hamilton extrapolation technique, the intraclass correlation coefficient was again employed.

Results

Applying the method of moments to 114

logarithmically extrapolated curves resulted in very good fits of equation 1 to the experimental curves; comparison of the observed and calculated points from each of the curves resulted in intraclass correlation coefficients between 0.9332 and 0.9990. By applying the method of least squares to the same data, significantly closer fits were obtained in every case, with intraclass correlation coefficients ranging between 0.9805 and 0.9996.

Figures 1 and 2 illustrate examples of a normal and a markedly abnormal dye curve fitted by the two methods. The original record,

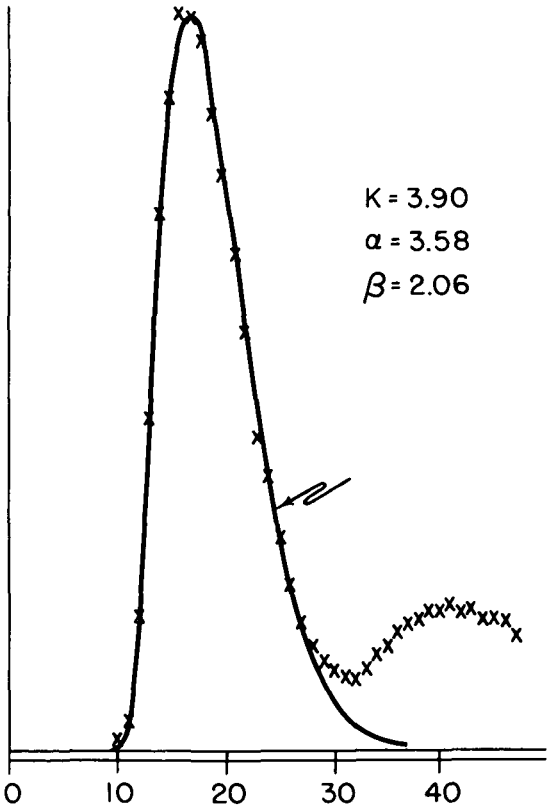

FIGURE 3

Comparison of a dye curve, plotted directly from the original photographic record without logarithmic extrapolation (indicated by crosses), with the curve derived from equation 1 (indicated by the solid line), using the method of least squares. Only concentrations indicated by the crosses preceding the arrow were used as data to derive the least squares fit. This illustrates that an excellent least squares fit can be obtained by direct application of equation 1 to the initial portion of experimental curves without logarithmic extrapolation.

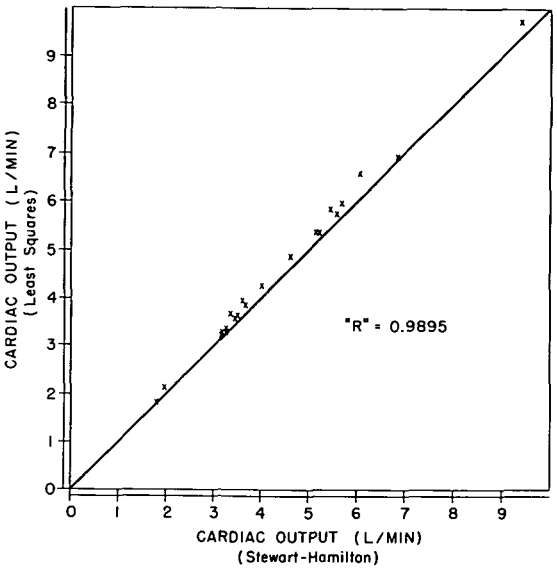

FIGURE 4

Cardiac outputs computed from 22 dye curves by the standard Stewart-Hamilton method (abscissa) and by integration of the corresponding function (equation 1), fitted by least squares (ordinate).

from which the data shown in figure 2 were derived, exhibited a moderate amount of arterial pulsation, which accounts for the irregular spacing of the plotted points (fig. 2A and D). The potential usefulness of the fitted curve as a "smoothing function" in computer applications is demonstrated by this figure.

When the initial portions of 22 curves were fitted *without extrapolation* by least squares (appearance time to a point on the downslope midway in time between the first peak and the first minimum), excellent curve fits were again obtained (fig. 3). Figure 4 shows the comparison between values for the cardiac output obtained by integration of the fitted curves with values obtained by the Stewart-Hamilton method.[14] There was a small, but statistically significant ($t = 6.69$, $P < 0.01$), average difference between the two estimates, the calculated values being slightly higher than the values obtained by extrapolation. If the least squares method was applied to the same curve both before and after logarithmic extrapolation, small differences in the resulting values of K, α, and β were noted.

In general, the values of α and β varied in opposite directions. Short curves with high peaks were associated with higher values of α and lower values of β (fig. 1), while prolonged abnormal curves usually had low values of α with high values of β (fig. 2). The values of β varied over a wide range from 1.08 to 8.48 (80% of the values were between 1.21 and 5.18), the larger values (greater than 5.2) being consistent indicators of prolonged curves with marked smearing of the downslope. The values of α varied between 1.69 and 6.24 (80% of the values between 1.69 and 4.17), except for one curve with a very rapid rise time and a steep downslope, for which the value of α was 12.29. The scaling constant, K, which reflects differences in the calibration factor and compensates for changes in the parameters, α and β, showed the widest variability (range 0.018 to 256.5, with one value of 0.00008 for the one rapid curve with α equal to 12.29).

Values of α, β, and K obtained by the method of moments differed, sometimes considerably, from the corresponding values determined by the method of least squares (e.g., figs. 1 and 2). Extreme examples of these discrepancies are illustrated in table 1. The fact that the fits were fairly close by the method of moments and very close by least squares, even though the values for α and β often showed considerable differences, indicates that the shape of the indicator curve is not highly sensitive to changes in the parameters, α and β.

TABLE 1

Extreme Examples of Discrepancies Between Parameter Estimates (See Text)

Curve no.		Method	Values	Intraclass correlation
1	α:	Moments	4.63	0.9362
		Least squares	7.81	0.9958
2	β:	Moments	12.20	0.9655
		Least squares	8.29	0.9885
3	K:	Moments	40.95	0.9577
		Least squares	16.12	0.9892

Discussion

THEORETICAL CONSIDERATIONS

Functions like that in (1) above are well-known in mathematical statistics and in theoretical physics, although they do not appear to have found extensive application in physiology. The function,

$$f(\tau) = \frac{1}{\beta^{\alpha+1}\Gamma(\alpha+1)}\,\tau^{\alpha}e^{-\tau/\beta}, \qquad (2)$$

$$(0 \le \tau < \infty;\ \alpha > -1)$$

$$\begin{cases} \tau = \text{random variable} \\ \alpha, \beta = \text{parameters of distribution} \end{cases}$$

represents a probability density function, which defines the distribution of a class of random variables important in statistical theory. $f(\tau)d\tau$ is the probability that the random variate, τ, will assume a value in the infinitesimal interval from τ to $\tau + d\tau$. Because integration of $\tau^{\alpha}\exp(-\tau/\beta)$ produces a gamma function (see Appendix; the integral is, in fact, equal to the denominator in (2)), members of this class of random variables are known as "gamma" variates.

If an indicator dilution curve (without recirculation) is considered equivalent to a density function in the mathematical sense, each ordinate must be divided by the total area under the curve, in order to transform each ordinate to a probability measure. The probability density function for the random variable, τ, where τ may now be used to designate transit time for individual indicator particles measured from the appearance time (i.e., $\tau = t - AT$, where t is the particle transit time from the time of injection and AT is the appearance time), can be expressed as,

$$f(\tau) = \frac{c(\tau)}{A} \qquad (3)$$

$$\begin{cases} c(\tau) = \text{indicator concentration at time, } \tau \quad (\tau > 0) \\ \qquad = 0 \quad (\tau \le 0) \\ A = \text{total area under the curve} \end{cases}$$

Let us examine the hypothesis that the random variable, $\tau = t - AT$, behaves like a gamma variate. This would require that the expressions for $f(\tau)$ in (2) and (3) be equal. That is,

$$f(\tau) = \frac{c(\tau)}{A} = \frac{1}{\beta^{\alpha+1}\Gamma(\alpha+1)}\,\tau^{\alpha}e^{-\tau/\beta} \qquad (4)$$

If $g(t)$ is used to represent the probability density function for the random variate, t, the transit time following injection, the expression for $g(t)$ can be easily derived from (4), using standard statistical mathematical methods.[20] * The resulting expression for the density function of t is

$$g(t)=\frac{C(t)}{A}$$

$$=\frac{1}{\beta^{\alpha+1}\,\Gamma(\alpha+1)}(t-AT)^{\alpha}\,e^{-(t-AT)/\beta} \quad (5)$$

$C(t)$ = indicator concentration at time, t $(t>AT)$
$=0$ $(t\leq AT)$
α, β = distribution parameters

A random variable, such as t, which has the probability density function shown in (5), has been called a "modified" gamma variate.[20] † If we multiply (5) by A, we obtain

$$C(t)=\left[\frac{A}{\beta^{\alpha+1}\,\Gamma(\alpha+1)}\right](t-AT)^{\alpha}\,e^{-(t-AT)/\beta} \quad (6)$$

Therefore, two consequences of the hypotheses that τ behaves like a gamma variate are 1) that the indicator transit time, t, would be equivalent to a "modified" gamma variate, and 2) that the indicator concentration could be expressed as a specific function of time shown in (6) above.

Since A, the area under a given dilution curve, is a constant, the function in (6) is a two-parameter family of curves. When specific values are given to the arbitrary distribution parameters, α and β, the shape of a given curve is specified. For convenience it is useful to represent the elaborate expression in brackets as a constant, K. In other portions of this paper, therefore, we have used the expression,

$$C(t)=K(t-AT)^{\alpha}\,e^{-(t-AT)/\beta} \quad (1)$$

where K can be considered as a "scale factor." While K is clearly a function of α and β, as well as of the area under the indicator curve, from the mathematical point of view, this point becomes of academic interest once appropriate values for α and β have been determined by curve-fitting techniques. The constant, K, can be expressed in terms of the peak concentration from the recorded dilution curve, C_p, and the parameter, α and β (see Appendix, equation 34):

$$K=C_p(e/\alpha\beta)^{\alpha} \quad (34)$$

Substitution of this expression into equation 1 gives the relation

$$C(t)=C_p(e/\alpha\beta)^{\alpha}(t-AT)^{\alpha}\,e^{-(t-AT)/\beta} \quad (7)$$

Although algebraically identical to equation 6, the elimination of the gamma function from the denominator makes the expression somewhat simpler to handle in the computer. The computer program for least squares curve-fitting employed in this study treated the function, $C(t)$, in the form given in (7), rather than that in (1) because the latter expression obscures the mathematical dependence of the constant K on the parameters α and β. For the solution by moments, α and β are determined from computed values $\Sigma tC(t)/A$ and $\Sigma t^2C(t)/A$ and the appearance time (see Appendix, equations 32 and 33), so that none of the equivalent functional expressions, (1), (6), or (7), are explicitly required for the solution.

The data in this report testify to the fact that functions from the family of curves (6) (or, equivalently, (1)) provide an excellent description of the mathematical behavior of the portion of indicator curves before recirculation occurs. Though the approach employed here is strictly empirical, the fits are close enough to warrant the conclusion that the hypothesis given above is, for practical purposes, correct. The close correspondence between experimental dye curves and fitted curves allows description of indicator transit time in terms of the well-known and convenient mathematical properties of gamma variates (see Applications, below).

It seems unlikely that it will be proved analytically that indicator transit time is strictly a modified gamma variate in the statistical mathematical sense (as it can be shown, for example, that the waiting time between emis-

* Pages 147 ff.
† Page 91.

sions of alpha particles from a radioactive substance is a gamma variate).[20] * There are, however, two mathematical models which have already been proposed which lead to expressions for $C(t)$ exactly equivalent to density functions of gamma variates. In Newman's paper,[2] equation 2a, derived for flow through two mixing chambers of equal volume, can be expressed in the form,

$$C(t) = \left(\frac{QI}{V^2}\right)(t - AT)\, e^{-(Q/V)\,(t - AT)} \quad (8)$$

$$\begin{cases} Q = \text{flow} \\ V = \text{volume of each mixing chamber} \\ I = \text{amount of dye injected} \end{cases}$$

If we note that A in our notation is analogous to I/Q, and if we substitute $1/\beta$ for Q/V, the following results are obtained:

$$C(t) = \left(\frac{Q^2}{V^2}\right)\left(\frac{I}{Q}\right)(t - AT)e^{-(Q/V)\,(t - AT)}$$

$$= \left(\frac{A}{\beta^2}\right)(t - AT)\, e^{-(t - AT)/\beta} \quad (9)$$

Since $\Gamma(2)$ is equal to 1, equation 9 is exactly equivalent to equation 6 above with $\alpha = 1$.

Warner[5] has suggested that diastolic volume in the chambers of the heart is probably the major determinant of smearing of the downslope of abnormal dye curves. The high values of β obtained in this study for curves exhibiting marked smearing suggest that chamber volume may also be a major determinant of the parameter, β. These observations, taken in conjunction with the formal analogy between β from (6) and V/Q of Newman's equation 2a, may indicate a very direct relation between β and cardiac chamber volume.

Sheppard[4] has discussed a "stochastic" model, where the indicator particles are considered to pass through a sequence of mixing compartments, all of which are alike. From this model is derived an equation, which, in the notation used in this paper, can be written as:

$$C(t) = \left(\frac{I}{Q}\right)\left(\frac{n}{(n-1)!}\right)\cdot [n(t - AT)]^{n-1} e^{-n(t - AT)} \quad (10)$$

(n = the number of mixing compartments)

As Sheppard points out, this expression is equivalent to a Poisson distribution curve. Simple algebraic transformation, and substitution of A for I/Q, result in the following expression:

$$C(t) = \frac{A}{\left(\frac{1}{n}\right)^n \frac{}{(n-1)!}}(t - AT)^{n-1} e^{-n(t - AT)} \quad (11)$$

If we let

$$\alpha = n - 1 \quad (12)$$

and

$$\beta = \frac{1}{n} \quad (13)$$

in equation 6 above, expression (11) becomes

$$C(t) = \frac{A}{\beta^{\alpha+1}(\alpha!)}(t - AT)^{\alpha}\, e^{-(t - AT)/\beta} \quad (14)$$

For Sheppard's model, where n is an integer, α can only take on integer values. Therefore (see Appendix A, equation 36), $\alpha! = \Gamma(\alpha + 1)$, so that expression (14) becomes identical to expression (6), and transit time in the stochastic model is precisely a gamma variate in the mathematical sense. For Sheppard's model to comply with the data reported in this study, the relations (12) and (13) would have to apply. Unfortunately, all of the values for β obtained by least squares in this investigation were greater than 1, a situation incompatible with relations (12) and (13) for integer values of n. The fact that the model does not provide an adequate representation of curves obtained in vivo was predicted by Sheppard.[4]

Inherent in the methods of determination of α and β, as carried out in this study, is an unfortunate dependence of the computed values on the observed appearance time. If the method of moments is used, the mean

* Pages 98 ff.

transit time (first moment) is computed by the usual formula, $\Sigma tC(t)/\Sigma C(t)$, and will not be in error, but the values for α and β will be subject to error if appearance time is incorrectly determined. Theoretically the appearance time would not have to be specified at all if the third moment from the experimental curve, $\Sigma t^3C(t)/\Sigma C(t)$, is used to obtain the required solutions for α and β (and, incidentally, for AT). In practice, however, the third and higher moments are critically dependent on the values for $C(t)$ far out in the tail of the curve, where reliable experimental observations cannot be made. Consequently, the solutions for α, β, and AT obtained by using the first three moments often fail to provide even a satisfactory fit to the curve.

If the least squares method is used to fit equation 7, with the observed appearance time introduced into the computer program as input (as was done to obtain the data presented in this report), the resulting solutions for α and β are again dependent on the observed appearance time. In this instance, unlike the case of the moments solutions, the computed mean transit time will not be identical to the value obtained from the standard formula, $\Sigma tC(t)/\Sigma C(t)$. As a matter of fact, the mean transit time, computed from the least squares parameters, will usually be about one or two seconds *less* than the value obtained by other methods. At first glance, one might suspect this would result from the usual tendency to overestimate the appearance time from the experimental curve, but this seems not to be the correct explanation for this discrepancy. Preliminary experience in this laboratory with another computer program for least squares estimation of α and β, which does *not* require specification of the appearance times, indicates that such a mathematical approach is quite workable and provides excellent curve fits (in contrast to the use of the third moment mentioned above). When this program is resorted to, the mean transit time, computed from the solved values for α, β, and AT, still is usually one or two seconds less than the conventionally-computed value. This indicates that the lower value for mean transit time does not result from an inaccurately observed value for appearance time.

The explanation for this finding seems to reside in a more fundamental difference between the gamma distribution curve and the Stewart-Hamilton exponential curve. Although the fits of the least squares curves are excellent up until the point where logarithmic extrapolation begins (small arrows in figs. 1 and 2), the gamma curve then passes below the logarithmically extrapolated curve. This is illustrated in the fourth panels of figures 1 and 2. This results in a lower computed mean transit time for the gamma curve than for the logarithmically extrapolated curve. Therefore, the gamma curve provides an excellent fit up to the onset of recirculation, but, from this point on, there is a small, but important, difference between the logarithmically extrapolated curve and the gamma curve. This consistent difference also explains the consistently smaller area for the gamma curves as compared to the logarithmically extrapolated curves. The difference in area probably accounts for the slightly higher cardiac output data obtained from the gamma curves (fig. 4). It will be of considerable interest to examine the correspondence between the gamma distribution curve and experimental curves obtained in situations where no recirculation is permitted to occur.

Equation 6, like the log normal equation of Stow and Hetzel,[13] remains an empirical representation for $C(t)$, despite the fact that the family of curves includes as special cases the two equations, 8 and 10, which were derived from simplified mathematical models. It differs from the log normal equation in having two, rather than only one, distribution parameters. This may imply a somewhat larger variety of curve shapes available for fitting to experimental data, but the relative merits of equation 6 and the log normal curve have not been tested experimentally. The logarithmic extrapolation of Stewart and Hamilton,[14] which is used as a basis of comparison in this study, is itself an empirical one. Further work is needed to define which, if any, of the presently available empirical methods for the mathematical

handling of dilution curves give an adequate description of the tail region of the curves.

After establishing that equation 1 can provide close fits to the initial portion of experimental curves without the necessity for logarithmic extrapolation, it is reasonable to seek a simpler method than least squares to accomplish this. For this purpose a method may be used, which makes use of the relationships between the appearance time, the time at which the concentration attains half its maximal value on the ascending slope of the dilution curve, and the time of maximal concentration. From these times, a ratio, r, can be formed, where,

$$r = (t_{p/2} - AT)/(t_p - AT) \qquad (15)$$

$$\begin{cases} t_{p/2} = \text{time of half-maximum concentration} \\ t_p = \text{time of peak concentration} \end{cases}$$

For any given value of r, the appropriate value of α can be obtained from the graph in figure 5. From the appearance time, the peak concentration, and the determined value for α, corresponding values for β and K can be easily found (see Appendix). Although in theory and simplicity of application, this method has much in its favor, it actually provides only rough approximations for the least squares values of α and β, primarily because it is difficult to determine accurately the appearance time from experimental records.

APPLICATIONS

The conclusions that indicator transit time may be considered equivalent to a modified gamma variate and that $C(t)$ may be expressed as a specific function of time (equation 1 above) lead at once to a consideration of possible applications of these concepts.

Advantage can be taken of the convenient mathematical properties of gamma variates. Knowledge of the values for K, α, and β for a given dye curve would allow use of any of the following formulas:

$$\int C(t)dt = K\beta^{\alpha+1}\,\Gamma(\alpha+1) \qquad (16)$$

$$\frac{\int tC(t)dt}{\int C(t)dt} = \text{mean transit time, } MTT = AT + \beta\,(\alpha+1) \qquad (17)$$

$$\frac{\int t^2C(t)dt}{\int C(t)dt} - (MTT)^2 = s^2 \text{ (Korner-Shillingford)}^{21} = \beta^2\,(\alpha+1) \qquad (18)$$

$$C_p = \text{peak concentration} = K(\alpha\beta/e)^\alpha \qquad (19)$$

$$t_p = \text{peak time} = AT + \alpha\beta \qquad (20)$$

If the method of moments is chosen to obtain α and β, there would be no need to make use of the relations above (equations 16 to 20), since the quantities on the left would have to be computed in the usual fashion and used as input to obtain the distribution param-

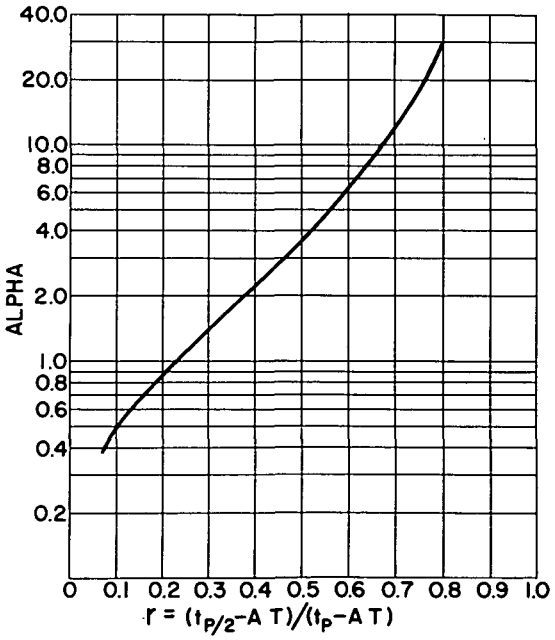

FIGURE 5

Theoretical relationship between the distribution parameter, α, and the ratio, r (see text). Abscissa represents a linear plot of r between 0 and 1. Ordinate, α, is graphed on a logarithmic scale, in order to facilitate the estimation of values in the lower range for α. Smaller values of α can be estimated with much greater accuracy from this graph, than higher values of α, because small changes in r, when r is large, are associated with large changes in α.

eters. On the other hand, if a computer is used to find values of α and β by the more elaborate least squares procedure, the quantities on the left of equations 16 to 18 and 20 are not used in the solution, and can be estimated using these relationships. In general, the values for the quantities on the left, as computed from the least squares parameters, will differ somewhat from the values obtained from curves extrapolated logarithmically in the standard fashion, because the extrapolations by the exponential and gamma curves are not identical, as discussed above. It is seen that the familiar integrals, used in many analyses of indicator dilution curves, may be dispensed with in computational work, if values for K, α, and β are obtained from a least squares computer program. The expression, $\Gamma(\alpha+1)$, found in equation 16, can be easily evaluated from tables of the gamma function.[22]

Recent discussions of the theory of indicator dilution curves have proposed the use of convolution integrals in the analysis of indicator curves, both with and without recirculation present.[1, 3, 4, 6–11] Zierler[9, 10] and others[6–8, 11] have reviewed these developments extensively. These treatments have produced valuable expressions in which $C(t)$ appears as an unknown function for which data from experimental curves must be substituted. When applied to dye curves with recirculation intact, the computations are difficult and laborious.[9] The availability of a relatively short mathematical expression for $C(t)$ offers promise of facilitating the experimental evaluation of these elegant mathematical models.

It is anticipated that the existence of the fitted function (1) will be very useful in the handling of experimental dye curves by digital computers. Standard mathematical computations, usually applied to experimental curves, may be performed by the computer, making use only of the derived parameters, K, α, and β, according to equations 16 to 20 above. The results in this study indicate that the cardiac output may be computed using $C(t)$ in (1) from intact curves without the necessity of logarithmic extrapolation to exclude recirculation. It should be noted that the fitted function acts as an excellent smoothing function, so that arterial pulsations which are frequently present in continuously-recorded dye curves, will constitute no problem in the on-line handling of experimental curves. In relation to on-line handling of indicator curves, it is possible to treat the appearance time in (1) as an unknown and apply a three-parameter least squares fitting procedure to the experimental curves, so that the appearance time (AT) emerges, along with α and β, as a solution of the curve-fitting procedure. This possibility is attractive, because it lessens the need for a perfectly flat base line. Preliminary observations in this laboratory indicate that this procedure is quite feasible and may, indeed, turn out to be the most effective use of equation 1 in computer applications.

Conclusions

An analytical expression for indicator concentration as a function of time would facilitate 1) theoretical analysis of arterial indicator dilution curves, 2) characterization of normal and abnormal curves, and 3) handling of experimental curves using high-speed computers. Indicator transit time has been shown to exhibit the mathematical properties of a general class of random variables, known as "gamma variates." Curve-fitting techniques were employed to show that the arterial indicator curves are equivalent to frequency distribution functions for this class of variables. The mathematical expression for these distribution curves provides us, at the same time, with an analytical representation for indicator concentration as a function of time,

$$C(t) = K(t-AT)^{\alpha}\, e^{-(t-AT)/\beta} \qquad (1)$$

Values of the two distribution parameters, α and β, determine the shape of the dilution curves. High values of β are consistent indicators of abnormal curves, with marked smearing of the downslope. Two equations for $C(t)$, which were previously derived analytically for simplified mathematical models, have been shown to be special cases of (1). One of these two equations provides suggestive evidence that cardiac chamber volume may be the

major determinant of the distribution parameter, β.

Excellent empirical curve fits may be obtained by the application of equation 1 to experimental curves. The known mathematical properties of the function (1) may be used as a convenient aid in the analysis of normal and abnormal indicator curves.

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Appendix

1. ORIGIN OF EQUATION 1

R. L. Evans [12] found that the family of curves,

$$c(\tau) = \tau^n e^{-a\tau} \qquad (21)$$

τ = time after appearance time
$c(\tau)$ = indicator concentration at time
a, n = arbitrary parameters

gave reasonable fits to indicator curves without recirculation, when integral values of n ($n = 2,3,4$) were tried. In order to fit a member of the family of curves (21) to an experimental curve, it is convenient to introduce a scale factor, K, to allow for changes in calibration factor (relating indicator concentration to amplitude of deflection in the recorded indicator curve). If we substitute α and $1/\beta$ for the parameters a and n respectively in (21), the correspondence between the expression (21) and the probability density function for a gamma variate (equation 2 above) becomes easily demonstrable. These changes result in the equation,

$$c(\tau) = K\tau^{\alpha} e^{-\tau/\beta} \qquad (22)$$

Noting that $\tau = t - AT$, we see that (22) is exactly equivalent to equation 1 above.

2. ESTIMATION OF THE DISTRIBUTION PARAMETERS, EMPLOYING THE METHOD OF MOMENTS

The moment-generating function for a given random variate, τ, designated as $M(\theta:\tau)$, is defined by the relation:

$$M(\theta:\tau) = E(e^{\theta\tau})$$

where E signifies "the expected value of" and θ is an arbitrary parameter.[20] * From the mathematical definition of "expected value," [20] † it can be shown that

$$E(e^{\theta\tau}) = \int_{-\infty}^{\infty} e^{\theta\tau} f(\tau)\, d\tau \qquad (23)$$

If the variate, τ, the indicator transit time measured from the appearance time, has the properties of a gamma variate, then its probability density function must be equivalent to

$$f(\tau) = \frac{1}{\beta^{\alpha+1}\,\Gamma(\alpha+1)} \tau^{\alpha} e^{-\tau/\beta} \quad (0 \le \tau < \infty)$$
$$= 0 \quad (-\infty < \tau < 0)$$

Substitution of this function into (23) and integration of the resulting expression leads to the relation, valid for all gamma variates,[20] *

$$M(\theta:\tau) = (1 - \theta\beta)^{-\alpha-1}$$

It can be shown [20] ‡ that, if $\tau = t - AT$,

$$M(\theta:t) = e^{\theta(AT)}(1 - \theta\beta)^{-\alpha-1} \qquad (24)$$

The moment-generating function derives its usefulness from the fact that the n^{th} moment of a given variate (around the origin) is exactly equal to the n^{th} derivative of the moment-generating function with respect to θ, evaluated at $\theta = 0$. If indicator transit time (seconds following injection) has the postulated frequency distribution function,

$$g(t) = \frac{C(t)}{\int C(t)\,dt} = \frac{1}{\beta^{\alpha+1}\,\Gamma(\alpha+1)} \cdot (t - AT)^{\alpha} e^{-(t-AT)/\beta} \qquad (25)$$

then we can find the first n moments of t conveniently from the first n derivatives of $M(\theta:t)$ in equation 24, each evaluated at $\theta = 0$. Thus, if μ'_n is used to indicate the n^{th} moment taken about the origin,[20] ‡

$$\mu'_1 = \int t f(t)\,dt = AT + \beta(\alpha+1) = MTT \qquad (26)$$

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* Page 211.
† Page 186.
‡ Page 213.

$$\mu'_2 = \int t^2 f(t)dt = (AT)^2 + 2(AT)\beta(\alpha+1) + \beta^2(\alpha+1)(\alpha+2)$$
$$= (MTT)^2 + \beta^2(\alpha+1) \quad (27)$$

More complex expressions can be derived for higher moments in similar fashion.

From experimental logarithmically-extrapolated dye curves, one can obtain estimates for the first and second moments of t, using the summation formulas familiar in many previous analyses of indicator dilution curves,

$$MTT = \mu'_1 = \frac{\Sigma tC(t)}{\Sigma C(t)} \quad (28)$$

$$\mu'_2 = \frac{\Sigma t^2 C(t)}{\Sigma C(t)} \quad (29)$$

The known values for the moments given by (28) and (29) can then be substituted for the integral expressions in (26) and (27), to obtain two simultaneous nonlinear equations in α and β:

$$AT + \beta(\alpha+1) = \mu'_1 \quad (30)$$

$$\mu'^2_1 + \beta^2(\alpha+1) = \mu'_2 \quad (31)$$

If appearance time is also considered an observable, these two equations are exactly solvable for α and β.

$$\alpha = \frac{(\mu'_1 - AT)^2}{\mu'_2 - \mu'^2_1} - 1 \quad (32)$$

$$\beta = \frac{\mu'_2 - \mu'^2_1}{\mu'_1 - AT} \quad (33)$$

Equations 32 and 33 give the values of the distribution parameters, α and β, from experimental data.

By setting $\frac{dC(t)}{dt}$ equal to zero in equation 1 above, it is easily shown that the peak concentration is equal to $K(\alpha\beta/e)^\alpha$. In this investigation we required that the maximum value of our fitted function be equal to C_p, the peak concentration of our experimental curves. From this and the solved values of α and β, the values for K were found from the equation,

$$K = C_p(e/\alpha\beta)^\alpha \quad (34)$$

From the method of obtaining the values of the first and second moments from experimental curves, it can be seen that this method of curve-fitting is not directly applicable to nonextrapolated curves, for which a more elaborate least squares curve-fitting procedure was required.[17, 18]

3. GAMMA FUNCTION

The gamma function of n, designated as $\Gamma(n)$, is defined as

$$\Gamma(n) = \int_0^\infty x^{n-1}e^{-x}dx \quad (35)$$

Once n is specified, $\Gamma(n)$ is equivalent to the area under the curve,

$$y = x^{n-1}e^{-x}$$

from $x = 0$ to $x = \infty$. Substitution of $(n+1)$ for n in equation 35 leads, by means of integration by parts, to the very useful relation,

$$\Gamma(n+1) = n\Gamma(n)$$

From this, one can easily show that for integral values of n,

$$n! = \Gamma(n+1) \quad (36)$$

To derive the expression for the area under the function, $\tau^\alpha exp(-\tau/\beta)$, mentioned in the text above, we can let $\alpha = n-1$, $\tau = \beta x$, $d\tau = (\beta)dx$, and proceed as follows:

$$\int_0^\infty \tau^n e^{-\tau/\beta}d\tau = \int_0^\infty (\beta x)^{n-1}e^{-x}(\beta)dx$$
$$= \beta^n \int_0^\infty x^{n-1}e^{-x}dx = \beta^n\Gamma(n)$$
$$= \beta^{\alpha+1}\Gamma(\alpha+1)$$

Except for integer values of n, $\Gamma(n)$ is not exactly integrable, but its values have been determined by numerical methods. Tables of the values of $\Gamma(n)$ are easily accessible.[22]

4. METHOD OF OBTAINING APPROXIMATE VALUES FOR α AND β FROM EXPERIMENTAL CURVES WITHOUT LOGARITHMIC EXTRAPOLATION

If we take the logarithms (base 10) of both sides of equation 1 and evaluate the resulting expression at the time of half-maximal concentration on the ascending slope of the curve, $t_{p/2}$ and at the peak time t_p we obtain:

$$\log(C(t_i)) = \log(K) + \alpha\log(t_i - AT) - [t_i - AT)/\beta] \bullet [\log e]$$
$$(i = p, p/2) \quad (37)$$

The two equations 37 may then be subtracted from one another and the terms rearranged. Noting that $(C_{p/2}/C_p = 1/2$, we obtain one equation from which both $C(t_i)$ and K have been eliminated:

$$\log(1/2) = \alpha \bullet \log[(t_{p/2} - AT)/(t_p - AT)] - [(t_{p/2} - AT)/\beta] \bullet [\log e] + [(t_p - AT)/\beta] \bullet [\log e] \quad (38)$$

Equation 20 above shows that,

$$\beta = (t_p - AT)/\alpha \quad (20')$$

so that equation 38 may be expressed in terms of α alone as,

$$-\log(2) = \alpha\log[(t_{p/2} - AT)/(t_p - AT)] - \alpha[(t_{p/2} - AT)/(t_p - AT)] \bullet [\log e] + \alpha[\log e] \quad (39)$$

If we let $\tau = (_{p/2} - AT)/(t_p - AT)$ and solve for α, we obtain

$$\alpha = \frac{-\log(2)}{\log(r) - r[\log e] + [\log e]} \quad (40)$$

Hence, if we determine the value of r from an experimental curve, we can solve for α. Figure 5 is a graph, from which α can be determined for any given experimental value of r. From the value of α and the appearance time, β can be found from equation 20'. The scale factor, K, can then be determined from equation 34.

The estimation of α, β, and K from the use of experimental values of r, AT, and C_p in association with the graph in figure 5 and equations 20' and 34, will usually provide reasonable curve fits of equation 1 to nonextrapolated experimental curves. The errors introduced in the measurement of AT, $t_{p/2}$, and t_p, however, make this a much less precise method for curve-fitting than the more elaborate method of least squares.

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