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Computer computations of cardiac output using the gamma function

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STARMER, C. FRANK, AND DAVID O. CLARK. *Computer computations of cardiac output using the gamma function.* J. Appl. Physiol. 28(2): 219–220. 1970.—A simplified method for fitting a gamma function to an indicator-dilution curve suitable for machine computation of cardiac output is presented. The method is more easily adapted toward determining recirculation than the classic Stewart-Hamilton technique. From the parameters measured by the curve-fitting procedure, the cardiac output, mean transit time, and other derived measures such as the effective mixing volume and s^2 described by Korner and Shillingford can be obtained.

indicator dilution; blood flow

A SIMPLE, RELIABLE METHOD using a digital computer for estimation of the cardiac output and other associated hemodynamic parameters from an indicator-dilution curve would be of value especially in an intensive or coronary care unit. The major problem in automating indicator-dilution analysis is the difficulty in removing recirculation from the curve. The classic Stewart-Hamilton method fits an exponential through the terminal portion of the dye curve, and recirculation is removed by assuming the dye concentration follows the fitted exponential decay. Automating this procedure requires the computer to pick out the points used to fit the exponential. At relatively low cardiac outputs, the computer program logic required to fit the best exponential is usually complicated. However, if another method which uses additional data were employed in the extrapolation procedure, perhaps the resulting extrapolation would improve.

It has previously been shown by Thompson and co-workers (5) that the family of curves represented by the function:

$$C(t_i) = k(t_i - t_a)^{\alpha} e^{-(t_i - t_a)/\beta} \qquad (1)$$

where k, α, and β are arbitrary parameters, t_a = appearance time, t_i = ith time, and $C(t_i)$ = indicator concentration at time t_i will give an excellent fit to indicator-dilution curves. The procedure for fitting *equation 1* to the indicator-dilution curve includes data from the initial portion of the experimental curve as well as data from the terminal portion. Thus a simpler program (than would be possible using the Stewart-Hamilton technique) to determine the extrapolation may be expected.

The purpose of this report is to present a simplified technique using a weighted least-squares procedure to fit *equation 1* to an indicator-dilution curve. The method is suitable for machine computation on many small computers and from the parameters k, α, and β determined by the fitting procedure, the cardiac output, mean transit time, mixing volume (1, 2, 4), and s^2 as described by Korner and Shillingford (3) can be easily determined.

METHOD AND RESULTS

The gamma function (*equation 1*) is a nonlinear model. To use a linear least-squares procedure, the model must be made linear. The gamma function can be linearized by taking logarithms yielding:

$$\ln C(t_i) = \ln k + \alpha \ln (t_i - t_a) - (t_i - t_a)/\beta$$

or

$$y_i = \mu + a_1 x_{i_1} + a_2 x_{i_2}$$

where

$$y_i = \ln C(t_i) \qquad a_2 = -\frac{1}{\beta}$$

$$\mu = \ln k \qquad x_{i_1} = \ln (t_i - t_a)$$

$$a_1 = \alpha \qquad x_{i_2} = t_i - t_a$$

To estimate the unknown parameters μ, a_1, and a_2 in the linear model, the least-squares regression method is used. This technique assumes that the experimental error in measuring the dependent variable ($\ln C(t_i)$) is constant. In the determination of indicator concentration, the error in $C(t_i)$ is approximately constant. However, since a logarithmic model is assumed, the error is no longer constant and it can be shown to be approximately inversely proportional to the squared indicator concentration. Resorting to a weighted least-squares analysis, let the weights be inversely proportional to the error variance:

$$w_i = C^2(t_i)$$

and compute

$$A_{11} = \sum_{i=1}^{n} w_i x_{i1}^2 - \frac{\sum_{i=1}^{n} w_i x_{i1} \sum_{i=1}^{n} w_i x_{i1}}{\sum_{i=1}^{n} w_i}$$

$$A_{12} = \sum_{i=1}^{n} w_i x_{i1} x_{i2} - \frac{\sum_{i=1}^{n} w_i x_{i1} \sum_{i=1}^{n} w_i x_{i2}}{\sum_{i=1}^{n} w_i}$$

$$A_{22} = \sum_{i=1}^{n} w_i x_{i2}^2 - \frac{\sum_{i=1}^{n} w_i x_{i2} \sum_{i=1}^{n} w_i x_{i2}}{\sum_{i=1}^{n} w_i}$$

$$A_{1y} = \sum_{i=1}^{n} w_i x_{i1} y_i - \frac{\sum_{i=1}^{n} w_i x_{i1} \sum_{i=1}^{n} w_i y_i}{\sum_{i=1}^{n} w_i}$$

$$A_{2y} = \sum_{i=1}^{n} w_i x_{i2} y_i - \frac{\sum_{i=1}^{n} w_i x_{i2} \sum_{i=1}^{n} w_i y_i}{\sum_{i=1}^{n} w_i}$$

then

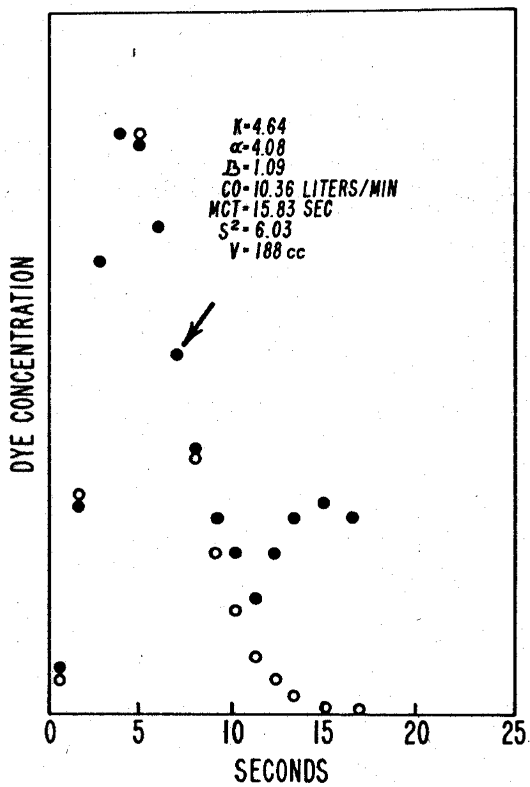

FIG. 1. Comparison of original indicator-dilution curve (●) with gamma function extrapolation (○). Arrow indicates last point used in analysis. Analysis yielded values of $k = 4.64$, $\alpha = 4.08$, $\beta = 1.09$. Cardiac output was 10.36 liters/min, mean circulation time = 15.83 sec, Korner-Shillingford $s^2 = 6.03$, and mixing volumes = 188 cm³.

$$D = A_{11}A_{22} - A_{12}^2$$

$$a_1 = \frac{A_{22}A_{1y} - A_{12}A_{2y}}{D}$$

$$a_2 = \frac{A_{11}A_{2y} - A_{12}A_{1y}}{D}$$

$$\mu = \left(\sum_{i=1}^{n} w_i y_i - a_1 \sum_{i=1}^{n} w_i x_{i1} - a_2 \sum_{i=1}^{n} w_i x_{i2}\right) \Big/ \sum_{i=1}^{n} w_i$$

From these

$$k = e^{\mu}$$

$$\alpha = a_1$$

$$\beta = -\frac{1}{a_2}$$

Using k, α, and β the following calculations are simplified: area under dye curve extrapolated to infinity

$$= \int_0^\infty C(t)\,dt = k\beta^{\alpha+1}\,\Gamma(\alpha + 1)^1$$

MCT = mean circulation time

$$= \frac{\int_0^\infty t\,C(t)\,dt}{\int_0^\infty C(t)\,dt} = t_a + \beta(\alpha + 1)$$

$$s^2 = \frac{\int_0^\infty t^2\,C(t)\,dt}{\int_0^\infty C(t)\,dt} - (\text{MCT})^2 = \beta^2(\alpha + 1)$$

$$\text{mixing volume} = V = Q\beta$$

where Q is the cardiac output in liters per second.

Indicator-dilution curves using indocyanine green dye were obtained from 35 patients initially diagnosed as having a recent myocardial infarction. Dye was injected into the right atrium. Blood was sampled from the radial artery and monitored through a cuvette densitometer. The resulting curves were digitized at 0.25-sec intervals either by hand or by an analog-digital converter. Analysis of these curves yielded cardiac outputs between 1.5 and 10 liters/min with mean transit times varying from 13 to 55 sec.

The gamma parameters were estimated with the above equations and the appropriate hemodynamic indicators were evaluated. Plotting the resultant "extrapolated" curve was accomplished by evaluating *equation 1* for each time associated with each input data point. Figure 1 illustrates a dye curve fitted by the least-squares procedure outlined above. The arrow marks the point on the downslope that is approximately equal to 70% of the peak dye concentration. Recirculation was assumed to start after the 70% point. Only the data between the appearance of dye (the 1st point in Fig. 1) and the 70% point were used in the fitting procedure.

The two methods yielded a mean difference of 400 cm³ (SD = ±390 cm³) with the gamma method consistently overestimating the Stewart-Hamilton calculated output. The correlation obtained by comparing the gamma method with the hand calculated Stewart-Hamilton technique was $r = 0.997$.

Conversion of the program to an online procedure requires determination of both the calibration factor and the appearance time. The calibration factor can be determined by observing the difference in the response of the analog-to-digital converter to a known concentration of indicator in blood and an undyed sample of blood. The appearance time is defined as that time after injection of the dye when the sampled dye concentration exceeds four standard deviations from the background "noise" determined immediately after dye injection. The digitized data are stored until the terminating point on the downslope of the curve is reached (70% of peak concentration). Using these data, gamma parameters are evaluated.

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[1] The gamma function can be evaluated by any of the available algorithms. See IBM 360 Scientific Subroutine Package Form H20-0205.