A Mathematical Model of Dilution Curves for Flow Study

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The purpose of this paper is to present a mathematical model of dilution curves obtained by precordial detection of concentration of an intravenously injected radioactive tracer. The analysis makes possible formulation of equations relating parameters of the curve to cofunctions of the curve, such as cardiac output, central circulating blood volume, and volume of heart chambers. The presentation is facilitated by a review of the graphical method of interpretation of these curves.

Stewart suggested determination of cardiac output by a dye-dilution method. Hamilton and his co-workers developed circulation studies based on observation of the varying concentration of an injected dye as it passed from the heart. If a small volume of concentrated dye is injected into a vessel emptying into the heart, the average concentration of the dye as it leaves the heart will be a function of the diluting volume which passed through the heart during the time of measurement. Thus, the parameters of the dilution curve permit, among other things, calculation of the cardiac output expressed as volume of flow per unit time. Since the total amount of material injected must eventually leave the heart, this amount may be equated to the product of the cardiac output, time of flow, and the average concentration of the material leaving the heart. The latter is equal to the product of the cardiac output and the instantaneous concentration of material integrated over the entire time of primary clearance. That is:

$$I = \int F \, dc$$

where \(I\) = amount of dye injected; \(F\) = cardiac output; \(c\) = concentration of dye in the blood. If the cardiac output \(F\) is constant during the time of measurement, it can be removed from under the sign of integration and the equation rearranged as

$$C. O. = \frac{I}{\int c \, dt}.$$

The usual technique for this basic procedure requires continuous recording of arterial concentration or assay of serial arterial-blood samples in order to determine the concentration of dye during the period of observation. Detection of an injected radioactive tracer by a counter placed over the precordium, as described by MacIntyre et al., permits the same determination without the more difficult arterial-blood sampling. By assay of a sample of venous blood drawn several minutes after the tracer injection, MacIntyre has shown, the term \(I\) in the last equation may be replaced by the product of the concentration in counts per minute (c.p.m.), recorded at the moment of drawing the blood, and the apparent volume of dilution, determined from in vitro assay of the blood sample and the amount of tracer injected. This equates the cardiac output to the product of volume units and counts per minute observed from a certain unknown volume, divided by the product of time units and the average counts per minute observed from that same unknown volume (the divisor being equal to the area under the dilution curve). MacIntyre's substitution permits estimation of cardiac output, in a volume-per-time expression, from measurement of three factors: the apparent volume of dilution of the tracer as determined from a venous blood sample, the instantaneous activity level recorded from the detector at the time of blood sampling, and

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the area under the dilution curve of primary circulation. The last factor is obviously the most difficult to determine accurately. Pre- cordial detection of the tracer as it passes through the heart usually yields a biphasic curve, regarding the tracer as it passes through the right heart and again as it passes through the left heart chambers.

By the graphical method, the area under the curve has been measured in the following manner: The area (B) of figure 1 has been calculated mathematically as the area under a descending exponential curve, and the area (A) has been measured with a planimeter. (In the appendix to this article there is described a simple electronic-integration measurement of area (A) which makes possible a quick, yet more accurate, determination of cardiac output.) In this method, it is assumed that the final downslope of the dilution curve approximates a true exponential curve. This assumption is valid as long as the left-heart curve (L.H. curve), caused by the second appearance of blood in the heart, is large relative to the right-heart curve (R.H. curve); therefore, the left side of the heart is favored in positioning the detector (see fig. 2).

In determination of central circulating blood volume, however, both L.H. and R.H. curves are necessary. According to the Stewart-Hamilton principle, the volume of dilution between two points is equal to the product of the rate of flow and the mean time of travel between these points. Thus, both L.H. and R.H. curves are needed, since the mean time between these curves represents the mean transit time for blood flow from the right side of the heart to the left. In figure 3, the R.H. curve (representing the tracer passing through the right heart) is extended by extrapolation of its descending slope under the L.H. curve. This descending part of the R.H. curve is then subtracted from the total (original curve) to yield the true L.H. curve, representing tracer flowing through the left-heart chambers. In the past, these two curves have been plotted on stiff paper, cut out, and balanced on a knife edge to determine the moment or center of gravity relative to the time axis of each curve, this being the location of the mean time of each curve. Hamilton suggested an approximate integration by
arithmetic which could be accomplished in 15 to 20 minutes with the aid of an adding and slide rule or a calculator. The mathematical model developed here makes possible easy determination of the center of gravity, or centroid, by use of a simple equation, described below, derived by integration by calculus. This equation is applicable to the curves obtained by the method discussed in this article.

Methods and Results

More than one hundred biphasic dilution curves recorded with the counter over the precordium were studied in order to determine a mathematical characterization for these curves. As the tracer was passed into, then pumped out of, the right side of the heart (a dilution chamber), a single curve was seen. It was predicted from single-chamber theory that the slope of falling activity (away from the crest of the curve) would be that of an exponential function, and this was observed to be true. On the other hand, a cylindrical bolus of tracer entering the chamber in a steady flow would cause a linear rise or build-up in concentration in the chamber. Excluding the effects of laminar or pulsating flow, a linear slope would be observed as a bolus of tracer entered the heart from a vessel. In this technique, the tracer was diluted to a volume of 3 ml. prior to injection. As it flowed to the heart, this 3-ml bolus was diluted to one which was considerably larger, yet small enough to pass into the heart in about 2.0 seconds. Laminar flow effect and pulsatile flow variations are insignificant with this method. The expected result is an approximately linear rise in these curves, and such a rise has been observed by us and by others. The slope of decreasing activity was observed to be an exponential function, as predicted.

With these characteristics of the total dilution curve, it became possible to formulate equations for calculation of area, to be used in cardiac-output determination, and of ordinal centroids (moments, or centers, of gravity). The latter were to be used in determination of mean time of travel between the two sides of the heart, data needed for calculation of central circulating blood volume.

The equation for calculation of the area was determined as follows (see fig. 4). The area under the rising slope of the I. I. curve was observed, with good consistency, to be linear. This slope is difficult to predict because of the variable complexities of the vascular channels through the lungs and the diminishing concentration of tracer in the blood leaving the right heart. The character of this particular slope was, therefore, empirically determined by observation of more than one hundred curves. Because of this empirical component in the analysis, dependent error was calculated. An error in judgment of the rising slopes great enough to cause an error of 10 per cent in the determination of the total area under both rising slopes of the curves, it was found, would result in an average error of 2.6 per cent in the calculated cardiac output. The slope of decreasing activity was observed to be an exponential function, as predicted.

As the blood passed through the lungs and entered the left side of the heart, the rising slope of the I. I. curve was observed, with good consistency, to be linear. This slope is difficult to predict because of the variable complexities of the vascular channels through the lungs and the diminishing concentration of tracer in the blood leaving the right heart. The character of this particular slope was, therefore, empirically determined by observation of more than one hundred curves. Because of this empirical component in the analysis, dependent error was calculated. An error in judgment of the rising slopes great enough to cause an error of 10 per cent in the determination of the total area under both rising slopes of the curves, it was found, would result in an average error of 2.6 per cent in the calculated cardiac output.

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The area under one curve of the biphasic dilution curve, therefore, is equal to:

\[ \text{area}_1 + \text{area}_2 = c \left( \frac{a}{2} + \frac{1}{m} \right) \]

The calculation was repeated for the other curve. Adding the results gave the total area under the biphasic curve. This total area was then employed in the formula used by MacIntyre et al.\(^4\)

\[ \text{C.O.} = \frac{(c + a \times \text{volume})}{\text{area under curve}} \]

In determination of central circulating blood volume, the mean transit time between L.H. and R.H. curves can be found by taking the difference between the moments or centers of gravity (ordinal centroids) of the curves.

Using the expression for ordinal position of a centroid:

\[ \bar{x} = \frac{\int x y \, dx}{\int y \, dx} \]

it was determined that the center of gravity (\(\bar{x}_1\)) for the triangle making up area 1 (under the rising slope), is one-third of the length of the base away from the vertical side (a vertical line from base to point of highest concentration).

Similarly, the center of gravity (\(\bar{x}_2\)) for area 2 (under the descending slope) was found to differ from the ordinate of origin by the length of the reciprocal of the slope. This ordinate of origin coincides with the vertical side of the triangle.

Knowing area 1 and area 2 and the centers of gravity (\(\bar{x}\)) of each permits calculation of the center of gravity of the curve made up of

\[ \bar{x} = \frac{x_1 A_2 - \bar{x}_1}{(A_1 + A_2)} \]

The difference between the centers of gravity of the two parts of this biphasic dilution curve can thus be determined. This equals the mean transit time of blood from the right heart through the lungs and into the left heart. The product of this time and the average flow rate during the time of measurement is equal to the central circulating blood volume (C.C.B.V.)\(^*\) (see Appendix).

These formulas for cardiac output and central circulating blood volume are easily set up on a work sheet to facilitate clinical applications. Such a work sheet is illustrated in figure 6, in the Appendix.

Comparison of results obtained by the graphic method with those obtained using these mathematical equations on the already replotted curves (avoiding the errors of replotting in the graphical method) shows good correlation, with no systemic error suggested.\(^\dagger\)

**Discussion**

An examination of dilution principles has permitted a mathematical representation of dilution curves recorded over the precordium when a tracer is injected into the blood. Based

\[^*\text{As used here, C.C.B.V. does not refer to circulating blood in the lungs alone. As observation of the tracer passing through a heart chamber is most probable in the center of mass of the mixed blood volume in it, the mean time of passage through that chamber is the mean time of passing through the center of mass of blood in the chamber. The mean time of transit between right- and left-heart chambers multiplied by the rate of flow, therefore, equals the average volume of circulating blood in one-half of the right-heart chambers, all of the pulmonary circulation, and one-half of the left-heart chambers. The difference in chronological phase shift during observation of the blood in the two halves of the heart could introduce only an error much too small to be observed (or none, if the volume of the left chambers equals the volume of the right).}\]

\[^\dagger\text{C.O. by this method (11 patients) averaged 104.1 cc./sec. (range 41.7 to 168.5); average by graphical method, 103.3 cc./sec. (43.3 to 168.5); average deviation was 4.2 per cent. C.C.B.V. by this method (10 patients) averaged 1,048 cc. (585 to 1,758 cc.); by the graphical method, 1,043 cc. (535 to 1,610 cc.); average deviation was 6.4 per cent.}\]

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DILUTION CURVES FOR FLOW STUDY

Figure 5

(Area "A") = total counts on register less background; (area "B") = c/m; total area = (area "A") + (area "B")

CO. = apparent volume of dilution X final counting level

total area under curve

Total register counts = ............................
Background X time = ... X ... = ...........................
(Area "A") = difference ............................
(Area "B") = c/m = ... / ... ............................
(Area "A") + (area "B") = ............................

C.O. = ...... L. X ...... c.p.m. ÷ ...... counts CO. = ...... L./min.

on this model, equations have been formulated for determination of cardiac output and central circulating blood volume. Modification may permit adaptation of this model and these equations to techniques in which the method of injection or detection is varied. When slower or more peripheral injection is used, the rising slope may require a different description, as the rising slope of the (single-peaked) arterial-sample curve is usually "slurred" and the crest of the curve made more round by the further dilution of tracer in transit.

As this system utilizes the first and second exponential decay slopes, its accuracy depends on recording a sufficient number of points to determine these slopes. When measuring a biphasic curve, it should be noted, this method uses the true exponential slopes in determining the area under the dilution curve, while the graphical and electronic-integration methods cannot. For estimation of cardiac output alone, electronic-integration measurement of a single-peaked curve is fast and accurate. For more complex studies of hemodynamics, using biphasic curves, the model and equations presented here permit accurate determinations and quantitative comparisons.

Certain relationships between parts of the biphasic curve have been observed. It is obvious that the rising and descending slopes will vary with the rate of flow and the extent of dilution of the tracer; these slopes will also be functions of stroke volume, residual volume, shunts, and, indirectly, valvular deformities. With several determinants capable of altering the shape of the curve, caution must be exercised in ascribing a change to any one alone. For example, the curve observed with aortic valvular insufficiency was similar to a low-cardiac-output curve, with high residual volume and low stroke volume, of any etiology. In normal subjects, the change in dilution and difference in residual volumes of the left- and right-heart chambers was reflected.
in a consistent 2:1 ratio of slopes of the R.H. curve to those of the L.H. curve. If the rising slopes fit this pattern but the descending slopes do not, or if the ratio is quite different from the approximately 2:1 usually observed, an alteration from the normal circulation is suggested. For instance, a left-to-right shunt will not alter the slopes of the R.H. curve, but may change the slopes of the L.H. curve. These relationships are being studied further in this laboratory, in an effort to determine if any changes may be characteristic of specific alterations in hemodynamics in pathological conditions.

Summary

The graphical method of estimating cardiac output and central circulating blood volume is reviewed. An electronic-integration modification is described for fast, accurate cardiac-output estimation. A mathematical representation of biphasic dilution curves is developed and, based on this analysis, formulas are proposed for determination of cardiac output and central circulating blood volume. Clinical application of this determination method is shown, and its advantages are discussed.

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Appendix

To measure cardiac output alone, a very accurate and quick method has been developed here. The only necessary addition to the equipment is an on-off switch which is used to activate the register on the counting equipment and a marker pen on the recorder simultaneously. This allows recording of the sum of the counts observed from the start of the dilution curve to some point on the last exponential descending slope, at which point the register counting is stopped. The sum is analogous to area "A," figure 5, and is equal to average c.p.m. multiplied by time in minutes; thus, multiplying net total counts for area "A" by 60 seconds/minute converts this figure to c.p.m.-seconds, the units of measurement of area "A" by planimeter or mathematical formula. This electronic-integration method of determining area "A" eliminates the inherent errors of graphic reproduction and planimeter measurement. Area "B" is determined (as in the graphical methods) by the equation:

\[ \text{area "B"} = c/m. \]

Calculation of central circulating blood volume is made as follows: the mean time of passing of each curve is determined by

\[ T_{in} = t_1 - a/3 + 1/m \left( a/3 + 1/m \right) \]

The product of the flow rate and the difference in the mean times of the curves is equal to the C.C.B.V.

\[ \text{C.C.B.V.} = \text{C.O.} \left( T_{m2} - T_{m1} \right). \]

The procedure is easily followed with the aid of a worksheet such as the one illustrated in figure 6.

Radiation Dosage Considerations

In calculation of radiation exposure from iodinated (I\(^{131}\)) human serum albumin, the total dose absorbed is dependent upon the volume of dilution assumed. Because of the closeness of blood vessel spacing, the assumption of whole-body dilution has been customary. On this basis, 20 µc. of iodinated (I\(^{131}\)) human serum albumin administered to a 70-Kg. patient would result in a maximum whole-body absorbed dose of 0.06 rad. Of this, approximately 0.036 rad would be received in the first week.

While this amount is very low, a reduction of approximately one-twentieth in the whole-body dose would be accomplished by use of a faster-clearing material, such as iodinated (I\(^{131}\)) iodipamide.

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Circulation Research, Volume IX, May 1961


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**BOOK REVIEW**

**The Arterial Wall.** Edited by Albert I. Lansing, A.B., Ph.D. Baltimore, The Williams & Wilkins Co., 1959, vi + 259 pages, illustrated. $7.50.

In this book, a cooperative effort by 13 authors, the structure, function, and metabolism of the arterial wall are discussed informatively and with imagination. The treatment of the subject is extensive: there are chapters on the microscopic anatomy of arterial vessels; on the chemistry and role of collagen, elastic tissue, and mucopolysaccharides; and on lipid metabolism of connective tissue as related to aging. The topic of the metabolism of arterial tissue and of smooth muscle is particularly well presented. There is also an expert summary of present knowledge about the mechanism of muscular contraction. To the great credit of the authors, the paucity of information about the metabolism and function of vascular tissue is emphasized repeatedly. If this book contributes toward greater efforts and interest in this field, it will serve a useful purpose.
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