Basic Concepts in the Determination of Vascular Volumes by Indicator-Dilution Methods

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The calculation of central (thoracic, pulmonary) blood volume from indicator-dilution data was introduced by Stewart1,2 and developed and applied mainly by Hamilton and his group.3,4 The so-called classical Stewart-Hamilton method was based on the premise that the product of flow rate and mean transit time defined the volume of the flow channels. Originally intuitive, this premise has recently been formally validated by Meier and Zierler.5 The classical method has been widely used, sometimes with misunderstanding.6-7 More recently, a mixing-chamber model developed to account for the form of the indicator-dilution curve has led to the introduction of a "slope-volume" method for describing pulmonary blood volume.8 Further attempts to partition the central blood volume into its cardiac and pulmonary components have led to the development of an indirect mathematical method based on the mixing-chamber model9 as well as to more direct experimental methods utilizing special locations of injection and sampling sites.8,10-12

It is the purpose of this paper to examine the fundamental concepts upon which these several methods are based. I shall begin with the classical method.

Classical Stewart-Hamilton Method

"The premise that in a properly defined system the product of flow rate and transit (or 'circulation') time exactly measures the volume of the flow channels was at the basis of Stewart's original development.1,2,13 Though often regarded with suspicion, there is nothing mysterious about this relationship. Dimensional considerations alone tell us that the product of a flow rate and a time defines a volume. If we now imagine any flow net whatsoever which includes a fixed volume, V, between its entrance and exit boundaries and through which fluid flows at a steady rate, Q, then there must exist some unique time, t, such that

\[ V = Q \times t \]  \hspace{1cm} (1)

We see that t is the time required for a volume of fluid equal to the flow net volume to enter or leave the system. Thus, if we choose the proper value of t, the classical Stewart-Hamilton volume prescription is true by definition. The real problem, therefore, is not the general validity of equation (1), but rather the experimental measurement of the proper t and the quasi-anatomic delineation of the entrance and exit boundaries of the flow net.

But even this is not mysterious if we choose a "properly defined system." Let figure 1 represent any single input-single output, open flow net with a volume, V, and no "stagnant pools" included between its entry and exit boundaries. Fluid enters and leaves the net at the steady rate, Q. Let us assume that this fluid is composed of a collection of small-volume elements which we can conveniently call "particles." Each particle is identified by its characteristic transit time, defined as the time required for it to travel between entrance and exit of the flow net. We shall assume that the frequency distribution of transit times among particles entering the net is identical at every instant (that is, stationary flow). Now it is clear that, in the steady state, the total volume of fluid within the net at any time, t, must consist of particles that entered during some previous interval but have not yet left. For example, consider particles of the ith kind identified by transit time, ti. At time t, the number of such particles in the flow net must

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be the number which entered between the times \((t - t_i)\) and \(t\), that is, during the immediately preceding interval equal to the transit time, \(t_i\), all such particles entering the net prior to \((t - t_i)\) having already left. But this number is just \(k(t_i)Qt_i\), where \(k(t_i)\) is the fraction of the total flow comprised of particles of the \(i\)th kind, that is, \(k(t_i) = \frac{Q}{Q} = \frac{O_i}{Q}\). The total volume of the net must then be the sum of a series of such terms, one for each species of particle

\[
V = Q \left[ k(t_1)t_1 + k(t_2)t_2 + \ldots + k(t_n)t_n \right]
\]

and we define

\[
\bar{t} = \frac{V}{Q} = \left[ k(t_1)t_1 + k(t_2)t_2 + \ldots + k(t_n)t_n \right].
\]

Passing from discrete particles to a continuous fluid medium having a continuous distribution of transit times, the sum in (3) becomes an integral

\[
\bar{t} = \int_0^\infty h(t)t \, dt
\]

(4). Thus, the \(t\) coordinate of the centroid of area under the density function is exactly that unique time whose product with flow yields the volume of the net. We call this time the "mean transit time." It is the average time required for fluid particles to traverse the flow net.

It is clear from equation (4) that if we knew the density function of transit times, \(h(t)\), we could calculate \(\bar{t}\). But how do we determine \(h(t)\) from an indicator-dilution curve? Let us consider two different cases.

**Single or "Slug" Injection.**—If a quantity, \(m_i\), of indicator is injected "instantaneously" to homogenously label the fluid entering the net at \(t = 0\), then it is clear that the indicator-dilution curve recorded at the exit is identical, except for an ordinate scale factor, with the density function of transit times. Hence, the \(t\) coordinate of the centroid of area under the \(C(t)\) curve will also be \(\bar{t}\)

\[
\bar{t} = \frac{\int_0^\infty C(t) \cdot t \, dt}{\int_0^\infty C(t) \, dt}.
\]

Equation (6) is the limiting form of the expression first given by Hamilton and associates to calculate mean transit time. Having determined \(\bar{t}\) and \(Q\) from our indicator-dilution curve, the product, \(Q\bar{t}\), will give the volume of our flow net, \(V\).

**Continuous Injection.**—When we look at this case, we find it possible to unify several seemingly different aspects of our problem in terms of a single general method. We note first that Hamilton and Remington and later Lewis treated the continuous infusion as a sequence of slug injections, and synthesized the continuous infusion curve by integrating the slug curve. This at once suggests a general method long used by electrical engineers to obtain the response of a linear system to an arbitrary forcing function in terms of its response to a "unit impulse." In the complex domain, this involves the multiplication of the Laplace transforms of system function and driving function, or,
in the real domain, the evaluation of a convolutional integral. Looking at the latter and specifying zero initial conditions, we note that if the response to a unit impulse (see below) is \( G(t) \), then the response, \( C(t) \), to an arbitrary forcing function, \( f(t) \), is given by the following convolutional integral

\[
C(t) = \int_0^t G(t - \lambda) f(\lambda) d\lambda. \tag{7}
\]

The unit impulse response, \( G(t) \), is called the system weighting or memory function because to evaluate \( C \) at any time, \( t \), the input value at all previous times, \( t - \lambda \), from \( \lambda = 0 \) to \( \lambda = t \), is weighted by the value of \( G(\lambda) \), that is, by the value that a unit impulse response initiated at \( t - \lambda \) would have at \( t \). The response to an impulse of magnitude, \( K \), is simply \( KG(t) \).

Now in the present context, a slug injection of \( m \) units of indicator into a flow of \( Q \) ml/sec. constitutes an impulse forcing of magnitude \( \frac{m}{Q} \). Hence, the concentration of the indicator at the exit, \( C(t) \), is

\[
C(t) = \frac{m}{Q} G(t) \tag{8}
\]

and if no recirculation is allowed, the system memory is just the density function of transit times between entrance and exit of the flow net. Hence the ordinate scale factor previously mentioned which transforms this density function into an indicator-dilution curve is \( \frac{m}{Q} \).

Next we note that a continuous infusion of indicator at \( n_i \) units/sec. can be treated as a step-function forcing of magnitude, \( \frac{n_i}{Q} \). Hence in equation (7), \( f(t - \lambda) = \frac{n_i}{Q} \), and the continuous-infusion curve (no recirculation) becomes

\[
C'(t) = \frac{n_i}{Q} \int_0^t G(t) \, dt. \tag{9}
\]

The integral in (9) is the limiting form of the finite sum used by Lewis to construct continuous infusion curves from slug curves. In general terms, it expresses the fact that the response of a linear system to a unit step function is the integral of its response to a unit impulse, that is, the integral of its weighting function.

Although we specified no recirculation in the examples given above, we do not have to do this. If we take \( G(t) \) as the response to a unit impulse including recirculation, then equations (8) and (9) will describe the slug and continuous-injection curves including recirculation, but \( G(t) \) will no longer be the distribution function of transit times between injection and sampling site. Alternatively, we can retain this distribution function as the system "memory" and include all recirculating indicator in \( f(t) \). The latter model was employed by Stephenson in the first basic theoretical analysis of the indicator-dilution method to appear. We note that the superposition principle embodied in equation (7) can be applied only to a linear system, and we achieve this in the present model by specifying stationary flow.

Now Lewis synthesized the continuous infusion curve in an attempt to avoid the use of "circulation time" in the calculation of central blood volume. His distrust of the transit times used by Stewart (appearance time) and by Nylin and Celander whom he quoted was certainly justified, but his method turns out to be just another way of calculating the correct mean transit time of Hamilton and co-workers whom he did not quote. Let us see how this comes about.

If no recirculation occurs during continuous infusion, a steady-state concentration, \( C'M \), will be attained at time, \( tM \), and the quantity of indicator in the system at this time will be \( C'MV \). But this quantity must equal the difference between the quantity injected up to this time, \( m_i tM \), and the quantity that has left the system, \( Q \int_0^{tM} C(t) \, dt \). Hence

\[
C'MV = m_i tM - Q \int_0^{tM} C(t) \, dt \tag{10}
\]

and if we divide through by \( C'M \), we obtain a formula for the calculation of central vol-
ume which apparently contains no "circulation time" term at all

\[ V = \frac{1}{C_M} \left[ \frac{t_M}{M} - Q \int_0^{t_M} C'(t) \, dt \right]. \]  

But now we note that since \( C_M = \frac{\dot{m}_1}{Q} \), we can put equation (11) into the following form

\[ V = \frac{Q}{C_M} \frac{t_M}{M} - \frac{1}{C_M} \int_0^{t_M} C'(t) \, dt. \]  

In this form it is clear that the bracketed term has the dimensions of time and must be numerically equal to the mean transit time defined in terms of the slug curve by equation (6). If this is so, we must be able to show that

\[ \int_0^{t_M} C(t) \, dt \quad \text{and this can readily be done by integrating } C(t) \, dt \text{ by parts} \]

\[ t_M \int_0^{t_M} C(t) \, dt = t_M - \frac{1}{C_M} \int_0^{t_M} C'(t) \, dt \]

and substituting in (13), we establish the identity

\[ \int_0^{t_M} C(t) \, dt = t_M C_M - \int_0^{t_M} C'(t) \, dt. \]

Thus it is clear that Lewis' method actually uses Hamilton and co-workers' mean transit time in disguise. This is a comforting confirmation of the "classical method" by an alternative derivation.

Some Practical Complications.—Thus far we have shown that in a "properly defined system" the classical Stewart-Hamilton procedure provides a convenient and valid method of calculating the volume of our flow net. Let us now pause to consider briefly some complications that arise when our system is not quite so properly defined as we would like.

First, in the real cardiovascular system, recirculation of indicator occurs rapidly enough to prevent the inscription of the pure density function of transit times between injection and sampling sites following a slug injection.

For the same reason, the continuous infusion curve does not reach a steady-state plateau but instead continues to rise as a ramp function. One of the major contributions of Hamilton's group was to introduce an extrapolation of the semilogarithmic down slope of the slug curve as a practical method of correcting for recirculation. Since the continuous infusion curve is the integral of the slug curve, an analogous, though somewhat less convenient, correction can be applied to it.

A second complication involves the fact that whereas our properly defined system possessed, among other conveniences, only a single input and a single output, the real cardiovascular system is at best a single input-many output system (inject into right atrium, sample from peripheral artery) and at worst a many input-many output system (inject into peripheral vein, sample from peripheral artery). How then can we define the product, \( Q_1 \)? In our original "well behaved" system, it is simply the volume of the net between injection and sampling sites, a quite satisfying definition. But in the single input-many output case, the volume must include each output channel up to the point at which the mean time is the same as that to the sampling site. Finally, in the many input-many output case, we must assume that the flow from the injection site is mixed in such a way that the fraction of it which leaves through any output channel is proportional to the flow in that channel. Then we can say that our calculated volume includes, in addition to those portions of the output channels just described, each input channel up to the point at which the average mean time to all the output points, weighted by the flow.
through each output channel, is the same as that to the sampling site.\textsuperscript{5} These latter two definitions of the measured volume are somewhat less satisfying, for the anatomic boundaries are only implicitly described. Nevertheless they are useful.

Complications arising from violation of some of the other assumptions characterizing our "properly defined system" have been discussed elsewhere.\textsuperscript{5}

Summary.—The classical Stewart-Hamilton method provides a simple and valid estimate of "central blood volume." One of its great practical advantages is the fact that its validity is independent of any theoretical assumptions about the form of the density function of transit times. The latter is determined purely empirically, although to do so requires accurate correction of the observed curves for recirculation. A possible disadvantage of the method is the fact that the "central blood volume" that it measures, although precisely definable in terms of "time distances," cannot be given very definite anatomic boundaries. This is not usually a serious defect, however.

Slope-Volume Method

The "slope-volume method" of Newman and associates\textsuperscript{8} developed out of attempts to find a theoretical model that would account for the form of the indicator-dilution curve. Its beginnings can perhaps be traced back to Hamilton and co-workers\textsuperscript{3} who first noted the empirical fact that the descending limb of the indicator-dilution curve following a slug injection was an exponential decay (no recirculation). Without presenting any theoretical analysis, they later pointed out that this behavior could be described by what they called the "compound interest law," and presented the following equation:\textsuperscript{4}

\[ C(t) = C_0 e^{-\frac{Q}{XV}t} \quad (16) \quad 0 < X \leq 1 \]

where \( Q \) is flow rate, \( V \) is the volume of the system, and \( X \) is a correction factor to account for incomplete mixing. Because of uncertainty in the value of \( X \), Hamilton and associates concluded that this equation could not be used to calculate \( V \). On the contrary, they used it to calculate \( X \) by substituting the value of \( V \) obtained by their "classical" method. It is apparent that equation (16) describes a single mixing chamber with instantaneous mixing in the virtual volume, \( XV \). It of course does not describe the first portion of the indicator-dilution curve, and Hamilton and associates did not pursue the matter further.

In 1950, Nylin and Celander\textsuperscript{18} derived an identical equation based on theoretical considerations. Although they described a model consisting of three chambers in series (right heart, lungs, left heart), their analysis was limited to the descending portion of the curve, and here they treated the model as though it were a single chamber. Like Hamilton and co-workers before them, they introduced a factor to account for incomplete mixing. Also, like Hamilton and co-workers, they did not use the slope of the descending limb to calculate \( V \) directly. However, they did use it to set a lower limit for \( V \). The rationale for this becomes clear from a consideration of equation (16). The slope, \( S \), of the semilog plot of this equation is

\[ S = -\frac{Q}{XV} \quad (17) \]

so that

\[ V = -\frac{Q}{XS} \quad (18) \]

If mixing were complete and instantaneous, then \( X = 1 \) and \( V = -\frac{Q}{S} \). However, if mixing were incomplete, then \( X < 1 \) and \( V > -\frac{Q}{S} \). Hence \( V \) must be at least as large as \(-\frac{Q}{S}\). To set an upper limit on \( V \), Nylin and Celander employed the classical method except that they erroneously used the mode instead of the mean transit time. They reasoned that the classical volume should be greater than the heart-lung volume since the time measured was needle to needle rather than right atrium to aortic root. Hence they took the arithmetic mean of "slope volume" and "classical volume" as the best estimate of heart-lung volume.

In 1951, the mixing chamber model was...
further developed theoretically by Newman and his colleagues. A major difference between this treatment and that of Nylin and Celander was that Newman and his group considered the entire curve and not just its descending limb. In so doing, they discovered that a three-chamber model plus an arbitrary dead time could generate indicator-dilution curves that resembled those of the prototype fairly well. They assumed complete and instantaneous mixing in each chamber and treated the case of a slug injection with no recirculation. Their equations may be developed in the following way, starting with a single generalized mixing chamber.

Let us consider a chamber of volume \( V_1 \) through which fluid flows at a steady rate, \( Q \) (fig. 2). An indicator, \( m \), is present in concentration \( C'_1(t) \) in the fluid entering \( V_1 \) and in concentration \( C_1(t) \) in the fluid leaving \( V_1 \). The quantity of \( m \) in \( V_1 \) is \( m_1(t) \). Then, if there are no other pathways for entry or exit of \( m \) from \( V_1 \), we can write

\[
\dot{m}_1 = Q(C'_1 - C_1). \tag{19}
\]

Equation (19) says that the rate of change of the quantity of indicator in \( V_1 \) is equal to the difference between its rate of entry, \( QC'_1 \), and its rate of exit, \( QC_1 \). Now in particular, if the entering fluid contains no indicator, \( C'_1 = 0 \), and if \( V_1 \) is an ideal mixing chamber (that is, produces instantaneous homogeneous mixing), then \( C_1 = \frac{m_1}{V_1} \). Under these conditions, (19) becomes

\[
\dot{m}_1 = -m_1 \left( \frac{1}{V_1} \right). \tag{20}
\]

Converting to concentrations by dividing through by \( V_1 \), we have

\[
\dot{C}_1 = -\frac{Q}{V_1}C_1, \tag{21}
\]

or

\[
\tau_1 \dot{C}_1 + C_1 = 0 \tag{22}
\]

where \( \tau_1 \equiv \frac{V_1}{Q} \), the time constant of the chamber. The solution to this first-order linear homogeneous differential equation satisfying the initial condition, \( C_1 = C_0 \) at \( t = t_0 \), is

\[
C_1 = C_0 e^{-\frac{t-t_0}{\tau_1}}. \tag{23}
\]

Newman and associates set \( C_0 \) equal to \( \frac{m_1}{V_1} \), where \( m_1 \) is the quantity of indicator injected as a "slug" at \( t = 0 \), and took \( t_0 > 0 \) to account for the finite appearance time observed in the prototype. Hence equation (23) defines the indicator concentration in \( V_1 \) for \( t \geq t_0 \). For \( t < t_0 \), \( C_1 = 0 \). We can interpret \( t_0 \) to mean that the injection site lies somewhere upstream from \( V_1 \), and that all of the indicator enters \( V_1 \) exactly \( t_0 \) seconds after its injection. We note that equation (23) for a single ideal mixing chamber is identical with that of Hamilton and associates and of Nylin and Celander except for omission of the mixing correction and inclusion of a dead time.

Now if we regard this first chamber as the analog of the right side of the heart, it is a simple matter to add a second to represent the lungs and a third to represent the left side of the heart. Since later stages influence neither the flow nor the concentration of earlier stages, the coupling between them will be "independent." However, for the later stages, the indicator concentration in entering...
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fluid will not be zero, but rather the output concentration of the previous stage. Hence we can at once write the following set of linear differential equations for the three-chamber model of figure 3:

\[ \tau_1 C_1 + C_1 = 0 \quad (22) \]
\[ \tau_2 C_2 + C_2 = C_1 \quad (24) \]
\[ \tau_3 C_3 + C_3 = C_2 \quad (25) \]

where \( \tau_1 = \frac{V_1}{Q} \), \( \tau_2 = \frac{V_2}{Q} \), and \( \tau_3 = \frac{V_3}{Q} \).

Assigning the initial conditions, \( C_1 = \frac{m_1}{V_1} \), \( C_2 = C_3 = 0 \) at \( t = t_a \), where \( m_1 \) is the quantity of indicator injected at \( t = 0 \), we obtain the following solutions for the indicator concentrations in each of the three chambers for \( t \geq t_a \):

\[ C_1(t) = \frac{m_1}{V_1} e^{-\frac{(t-t_a)}{\tau_1}} \quad (26) \]
\[ C_2(t) = \frac{m_1}{V_1-V_2} \left( e^{-\frac{(t-t_a)}{\tau_1}} - e^{-\frac{(t-t_a)}{\tau_2}} \right) \quad (27) \]
\[ C_3(t) = \frac{m_1 V_1}{(V_1-V_2)(V_1-V_3)} e^{-\frac{(t-t_a)}{\tau_1}} - \frac{m_1 V_2}{(V_1-V_2)(V_2-V_3)} e^{-\frac{(t-t_a)}{\tau_2}} - \frac{m_1 V_3}{(V_2-V_3)(V_1-V_3)} e^{-\frac{(t-t_a)}{\tau_3}} \quad (28) \]

For \( t < t_a \), \( C_1 = C_2 = C_3 = 0 \). Sample indicator-dilution curves generated by these equations on an operational analog computer are shown in figures 4 and 5. The resemblance of \( C_3(t) \) to indicator-dilution curves obtained in man (no recirculation) is apparent.

Newman and associates pointed out that if \( \tau_2 \gg \tau_1 \) and \( \tau_3 \), the first and third exponential terms of equation (28) would die out relatively rapidly, and that the semilogarithmic down slope of the indicator-dilution curve should be equal to \( -\frac{1}{\tau_2} \). Since \( \tau_2 = \frac{V_2}{Q} \), \( V_2 \), the volume of the lungs, could thus be calculated from the down slope and \( Q \).

How valid is this "slope-volume" method and how satisfying is the serial mixing-chamber model as a theoretical basis for the observed form of the indicator-dilution curve? It is of interest, first, to point out the various interpretations that have been assigned to the volume so calculated. If complete mixing were assumed, then Hamilton's group would have apparently equated the slope volume to the classical volume, Nylin and Celander would have equated it to a somewhat lesser volume, that is, heart plus lungs, and finally Newman's group would have equated it to a still smaller volume, that of the lungs alone (although they later began to call it "central" volume). The experimental fact is that the slope volume averages about 30 per cent to 50 per cent of the classical volume in man, and therefore measures only a part of the latter. But what part?

Newman and associates believed that sup-
curve lies between that for pulmonary-artery injection and that for the pulmonary-vein injection. But when we examine the figures, it turns out that the slope volume from pulmonary vein to carotid artery averaged approximately 60 per cent of that from right atrium to carotid artery, which hardly agrees with the theory. The results recently reported by Marshall and associates point up the same quantitative discrepancy. Although experiments were done in which injection was made into the pulmonary artery and concentrations monitored in the left atrium in order to determine the form of the lung dilution curve,
apparently no lung volumes were calculated from these curves for direct comparison with slope volumes calculated from right atrium to carotid artery curves.

But perhaps the most disturbing result of all is the behavior of the dead time. In the three-chamber model of Newman and associates, all of the dead time resides in a delay line located proximal to the entrance of the right side of the heart. Therefore if we inject our indicator anywhere distal to this point, there should be no dead time at all. But of course this is not what was actually observed. Sampling from the carotid artery, there was a dead time of about 1 second for aortic-root injection, 1.2 seconds for pulmonary-vein injection, 3.3 seconds for pulmonary-artery injection, and 3.5 seconds for right atrial injection. Obviously the flow net from right atrium to aortic root does not behave as theory demands.

This is hardly surprising. Although it is relatively easy to conceive of the left and right sides of the heart as mixing chambers, it is quite difficult to imagine that the flow net between them behaves as one. Of course it would be a simple matter to add more delay lines to the model to account for the experimental observations. We need only translate \( C_i(t) \) an additional \( t_k \) units and \( C_f(t) \) an additional \( (t_k + t_c) \) units along the time axis and to include still another delay from \( C_f(t) \) to the sampling point. But as soon as we do this, the interpretation of the slope volume becomes obscure. Delay lines within the system must be associated with some portion of the vascular bed, and these would be excluded from the slope volume. Thus, in a flow system characterized by a “lag exponential” dilution curve (delay line and single mixing chamber in series), the slope volume yields the volume of the mixing chamber only, whereas the classical volume yields both. If \( t_a \) is an appreciable fraction of \( \tau \), these estimates of volume will be quite different, and this appears to be true for all of the dilution curves reported in the study by Newman and associates. This no doubt explains why his values for central volume were so low.

In summary, we can say that the slope-volume method measures some fraction of the classical volume, but that this fraction cannot be assigned very definite anatomic boundaries. The theory itself is not very satisfying for there is no doubt that the pulmonary vascular bed is not in fact a single ideal mixing chamber. Nevertheless, the work of Newman and associates represent a pioneering effort to account for the form of the indicator-dilution curve on basic theoretical grounds. From this viewpoint it is valuable even though the particular model proposed may ultimately be replaced by a more satisfactory one. Perhaps we can conclude, as Sheppard has done, that the general resemblance between theoretical and experimental curves is the result of a statistical accident. More will be said about this in the next section.

**Theoretical Stochastic Models**

In the discussion of the classical method a convolutional integral was used to express the output concentration in terms of a system weighting function, or response to unit impulse. This weighting function was identified with a statistical property of the system, that is, the density function of transit times. Then it was noted that Newman’s group had developed a theoretical model to account for the form of the indicator-dilution curve. The weighting functions for their one, two and three-chamber models can be obtained easily by dividing equations (26-28) by \( \frac{V_n}{Q} \). Is there a statistical model that will yield these same weighting functions?

The appropriate stochastic model was identified by Sheppard. We may regard each mixing chamber as a “state” characterized by an “exponential holding time” from which indicator particles attempt to escape in random fashion. The probability that the time required for escape from state \( n \) will exceed \( t \) is just \( e^{-t/\tau_n} \), where \( \tau_n = \frac{V_n}{Q} \), and the density function of transit times for passage “through” state \( n \) is just \( \frac{1}{\tau_n} e^{-t/\tau_n} \). The lat-
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Unit block diagram.

The weighting function of Newman’s single-chamber model. A series of such chambers with different \( \tau \) values is an example of a “pure birth process,” the same model that applies to radioactive transmutation chains.24 If all of the \( \tau \) values are identical, then the model reduces to a simple Poisson process. The mean transit time for passage through state \( n \) is just \( \tau_n \), and for passage through a series of such states it is \( \sum_{i=1}^{n} \tau_i \).

Interpreted in this way, Newman’s model requires us to picture each of the dye particles as moving through the central flow net in three large sudden jumps with relatively long intervening pauses. A more satisfactory statistical picture would perhaps be provided by a model in which the particles traversed the net via a very large number of rapidly occurring small jumps. The appropriate stochastic model is a “random walk with drift,” although some of its features can be approximated by a Poisson process that includes a large number of short holding times.23 Sheppard has used the latter model to explore the problem of recirculation. In so doing, he made use of the Laplace transform method to evaluate a convolutional integral, as had Stephenson27 before him. In the next section this treatment will be extended to provide a general approach to the indicator-dilution problem in terms of the block diagram-transfer function method used by electrical engineers to describe the performance of linear feedback systems.25

**Block Diagram-Transfer Function Approach**

Since this approach is directly related to the Laplace transform method for the solution of linear differential equations, we need to briefly describe this method. In essence, it consists of transforming differential equations in the real variable, \( t \), into algebraic functions of the complex variable \( s \) (direct Laplace transform), manipulating the latter algebraically to obtain a solution in terms of \( s \), and finally transforming this solution back into the time domain (inverse Laplace transform). The transform process itself need not concern us, but we may note that tables of transforms for most of the common operations and functions are available. In the discussion to follow, we shall assume that our system always starts from “rest,” that is, from initial conditions of zero.

Now let us define a “block” as a system that operates on an input to produce an output. Then let us define the “transfer function” of a block as the Laplace transform of its weighting function. In figure 6, \( G(s) \) is the transfer function of the block, while \( C_a(s) \) and \( C_0(s) \) are the Laplace transforms of input and output functions respectively. Now the relationship between the input and output of any such block is simply

\[
C_0(s) = G(s)C_a(s)
\]

that is, in the \( s \) domain the output of any block is simply the product of its transfer function and its input (driving, forcing) function. Since the transform of a unit impulse is unity, the response to unit impulse is simply \( G(s) \). We note further that if \( C_0(s) \) enters a second block whose transfer function is \( H(s) \), then the output of the second block, \( C_R(s) \) is

\[
C_R(s) = H(s)C_0(s) = G(s)H(s)C_a(s) = W(s)C_a(s).
\]

Thus the over-all transfer function of a
series of blocks is just the product of the component transfer functions.

Now it happens that the inverse transform of (29) is the following convolutional integral:

$$C_0(t) = \int_0^t G(\lambda)C_a(t-\lambda) \, d\lambda. \quad (31)$$

We have already encountered this integral in our discussion of the classical method and have interpreted its meaning in terms of the response to unit impulse, that is, the weighting function, $G(t)$. Now we find that this integral is most easily solved by transforming the integrand to the complex product, $G(s)C_a(s)$, and then transforming the result, $C_0(s)$, back into the time domain.

We are now ready to formulate our indicator-dilution problem in these terms. In the block diagram of figure 7, $G(s)$ is the "forward" transfer function from injection site to sampling site, and $H(s)$ is the "feedback" (or recirculation) transfer function from sampling site to injection site. The function, $C_f(s)$, is the Laplace transform of the forcing (that is, the indicator-injection) function. In the open-loop system of figure 7A, the "actuating" signal, $C_a(s)$, is equal to $C_f(s)$, but in the closed-loop system of figure 7B, $C_a(s)$ is the sum of $C_f(s)$ and $C_R(s)$. The latter is the feedback signal, that is, the concentration of recirculating indicator. Note that this is a positive feedback system. It is now a simple matter to write the equations for the system in terms of transfer functions. If we define $W(s) = G(s)H(s)$, we have for the open loop (no recirculation)

$$C_0(s) = G(s)C_n(s) = G(s)C_f(s) \quad (32)$$

$$C_R(s) = W(s)C_a(s) = W(s)C_f(s). \quad (33)$$

We may call $G(s)$ the open-loop output transfer function and $W(s)$ the open-loop feedback transfer function. We note that although (32) and (33) expressed in terms of $C_a(s)$ hold equally well for open or closed loop, the alternative expressions in terms of $C_f(s)$ hold only for the open loop where

![FIGURE 7](image-url) Block diagrams for indicator-dilution system. A. Open loop, that is, no recirculation. B. Closed loop, that is, recirculation.

![FIGURE 8](image-url) Solutions for eight-chamber Poisson model for slug injection with open loop. From top to bottom, $C_1(t)$, $C_2(t)$, $C_3(t)$, $C_4(t)$, $C_5(t)$, $C_6(t)$, $C_7(t)$, $C_8(t)$. Concentrations in arbitrary units (with $C_1$ scale compressed 4:1), time in seconds. Parameters: $Q = 6$ L/min., $V_1 = V_2 = \ldots = V_8 = 625$ ml. ($\tau = 6.25$ seconds).
FIGURE 9
Same as figure 8, but for closed loop.

\[ C_\theta(s) = C_r(s). \] For the closed loop, \[ C_\theta(s) = C_r(s) + C_H(s), \] and so we obtain

\[ C_\theta(s) = \frac{G(s)}{1-W(s)} C_r(s) \] (34)
\[ C_H(s) = \frac{W(s)}{1-W(s)} C_r(s) \] (35)

and we may call \[ \frac{G(s)}{1-W(s)} \] the closed-loop output transfer function, and \[ \frac{W(s)}{1-W(s)} \] the closed-loop feedback transfer function. Hence if we know \( G(s) \) and \( W(s) \), we can obtain the responses to any arbitrary injection function. It is of interest that the injection functions that have so far been explored are the impulse (slug injection), the step function (continuous injection), and the ramp, the last by Andres and associates when they assumed this form for \( C_R(t) \) during continuous infusion. All of these are standard input functions in system-response theory.

Now we can say that the classical method is content to determine \( G(s) \) empirically. Newman's model assigns a particular theoretical form to \( G(s) \), namely

\[ G(s) = \frac{1}{(r_1s + 1)(r_2s + 1)(r_3s + 1)}. \] (36)

In control-system terminology, Newman and associates took \( G(s) \) as three "first order
lags" in series. Finally the Poisson process model used by Sheppard takes \( W(s) \) as \((n + k)\) equal first-order lags in series and assigns \( n \) of them to \( G(s) \) and the rest to \( H(s) \)

\[
G(s) = \frac{1}{(\tau_s + 1)^2} \\
H(s) = \frac{1}{(\tau_s + 1)^4}
\]

Indicator-dilution curves generated by this model on an operational analog computer with \((n + k) = 8\) are shown in figures 8-11.

We can say that the aim of future studies will be to obtain forms for \( G(s) \) and \( H(s) \) which, in ever increasing measure, are both conceptually satisfying and empirically useful. If, however, a sufficiently realistic description requires relaxation of the linearity restriction, then this simple and convenient approach is no longer applicable.

Ventricular Volumes

As we have already noted, the central blood volumes that combined indicator-dilution and x-ray technics was suggested by Lagerlöf and associates. As we have noted previously, the slope volume that Nylin and Celander used to set the lower limit of thoracic-pool volume was later interpreted by Newman and associates to be the volume of the largest mixing chamber in this pool, that is, the lungs. We have pointed out that the validity of this interpretation is very much in doubt. This is unfortunate, for if we could accept Newman’s three-chamber model at face value, then there is available a mathematical method for obtaining not only the lung volume, but the volumes of left and right sides of the heart as well from the same dilution curve. This method, based on Newman’s model, was suggested by Lewis, and will be described here briefly.

First, we rewrite equation (28) for Newman’s three-chambered model omitting the dead time and using a simplified notation

\[
C_3(t) = k_1e^{-t/\tau_1} - k_2e^{-t/\tau_2} + k_3e^{-t/\tau_3}
\]

where \( k_1 = \frac{m_1V_1}{(V_1-V_2)(V_1-V_3)} \), \( k_2 = \frac{m_2}{(V_1-V_2)(V_2-V_3)} \), and \( k_3 = \frac{m_3V_3}{(V_2-V_3)(V_1-V_3)} \).

Then, having determined flow by the usual method, we determine the slope and intercept of the semilog down slope. If the latter is assumed to be determined by the lungs, we thereby obtain \( V_2 \) and \( k_2 \). Now we direct our attention to the peak of the observed curve, that is, to the instant, \( t = t_p \).

At this instant, \( \dot{C}_0(t_p) = 0 \), and since according to equation (25), \( \dot{C}_3(t) = \frac{1}{\tau_3} (C_2-C_3) \), it is clear that \( C_0(t_p) = C_2(t_p) \). Hence we can account for the total amount of injected indicator, \( m_1 \), at this instant as follows

\[
m_1 = Q \int_0^{t_p} C_0 dt + C_3(t_p)(V_2+V_3) + m_1e^{-t_p/\tau_3}
\]

where the first term on the right represents indicator that has left the system, the second term the amount present in \( V_2+V_3 \), and the third the amount in \( V_1 \). Rearrange-
After integrating (40) to obtain $V_3$, we have

$$V_3 = \frac{1}{C_2(t_0)} \left[ -\int_0^{t_0} C_2 \, dt - \frac{m_i}{C_2(t_0)} e^{-t_0/r_1} \right] - V_2$$

and defining an "approximate" volume, $V_3$, as follows

$$V_3' = V_3 + \frac{m_i}{C_2(t_0)} e^{-t_0/r_1} \tag{42}$$

we rewrite (41) as

$$\frac{1}{C_2(t_0)} \int m_i - Q \int_0^{t_0} C_2 \, dt - V_2. \tag{43}$$

Since all terms on the right are now known, we can calculate $V_3'$. Next we note that the solution for $C_2(t)$ in this model (omitting the dead time) is

$$C_2(t) = \frac{m_i}{V_1 - V_2} \left( e^{-t/r_1} - e^{-t/r_2} \right) \tag{44}$$

and solving for $V_1$

$$V_1 = V_2 - \frac{m_i}{C_2(t_0)} e^{-t_0/r_1} + \frac{m_i}{C_2(t_0)} e^{-t_0/r_1} \tag{45}$$

Noting again that $C_2 = C_0$ at $t = t_0$, we once more define an approximate volume $V_1'$,

$$V_1' = V_2 - \frac{m_i}{C_2(t_0)} e^{-t/r_2} \tag{46}$$

and rewrite (45) as

$$V_1' = V_2 - \frac{m_i}{C_2(t_0)} e^{-t/r_2} \tag{47}$$

Once again, all of the terms on the right are known and we can calculate $V_1'$. Finally, we can determine the "correction term,"

$$x = \frac{m_i}{C_2(t_0)} e^{-t_0/r_1}, \tag{48}$$

which appears in both (42) and (46). To do so, we write

$$k_2 = \frac{m_i V_2}{[(V_1' + x) - V_3'][V_2 - (V_3' - x)]} \tag{49}$$

and solving for $x$, we obtain the quadratic

$$x^2 + (V_1' - V_2)x + \left[ \frac{(V_1' - V_2)(V_2 - V_3') + m_i V_2}{k_2} \right] = 0. \tag{49}$$

Having calculated $x$, we can finally obtain $V_1$ and $V_3$.

Lewis applied his method to 13 curves obtained in 10 rabbits. His slope volume, $V_2$, averaged 72 per cent of the classical volume determined on the same curves, a much higher figure than that obtained in man, and his sum $(V_1 + V_2 + V_3)$ averaged about 7 per cent higher than the classical volume.

We must interpret this to mean that the appearance time was negligibly small in these experiments, and this was certainly true for the single experimental curve illustrated. Unfortunately, it does not appear to be true either in man or dog.

Finally, let us consider a more direct method of measuring ventricular volumes in which indicator is injected directly into the ventricular chamber and concentrations are monitored at the ventricular exit. If any components of the flow net within the classical central volume behave as simple mixing chambers, the ventricles are the most likely candidates. True, the volume of these chambers varies with the cardiac cycle, but this can be easily taken into account and might help to ensure adequate mixing. Beginning with Bing and associates, a number of mathematical models have been proposed for the dilution process in the ventricle. Although formulated with varying degrees of rigor and completeness, all of these models are basically similar to the one we shall present below.

Let us begin by assuming (1) a steady-state cardiac cycle characterized by constant frequency ($F$), stroke volume ($V_s$), residual volume ($V_r$), and thus diastolic volume ($V_d$); (2) injection of $m_i$ units of indicator in entering blood. Then from elementary dilution principles, the concentration of indicator in the ventricle; and (4) no indicator in entering blood.
first stroke volume following injection will be

$$C_1 = \frac{m_i}{V_d} \quad (50)$$

and in the second

$$C_2 = C_1 \left( \frac{V_c}{V_d} \right) \quad (51)$$

and in the third

$$C_3 = C_2 \left( \frac{V_c}{V_d} \right) = C_1 \left( \frac{V_c}{V_d} \right)^2 \quad (52)$$

or, in general,

$$C_n = C_{n-1} \left( \frac{V_c}{V_d} \right) = C_1 \left( \frac{V_c}{V_d} \right)^{n-1}, \quad (53)$$

for \((n-1) \frac{1}{F} \leq t < n \frac{1}{F}\).

Equation (53) defines the "discontinuous exponential decay" curve illustrated in figure 12. It is easy to obtain all of the ventricular volumes from these equations. Thus from (50), the diastolic volume is simply

$$V_d = \frac{m_i}{C_1}, \quad \text{as noted by Holt.}$$

Then from (53) it is evident that the residual volume, \(V_r\), is

$$V_r = V_d \left( \frac{C_n}{C_{n-1}} \right). \quad (54)$$

Having obtained \(V_d\) from (50) and \(V_r\) from (54), their difference, \(V_d - V_r\), is just the stroke volume \(V_s\). Although this method is theoretically sound, it depends on the precise measurement of \(C_1\), and this is just the portion of the experimental curve that might be expected to deviate most widely from the theory. Thus, it may be difficult to time the injection precisely enough. Holt has therefore employed a different method of calculation. The cardiac output, \(Q\), is determined from the ventricular dilution curve by the usual Stewart-Hamilton method and the average stroke volume is then \(Q/F\). Equation (53) is then solved for \(V_d\) in terms of \(V_s\)

$$V_d = \frac{V_s}{\left(1 - \frac{C_n}{C_{n-1}}\right)} \quad (55)$$

and \(V_d\) is calculated from (55) by using an average value for the ratio \(C_n/C_{n-1}\) obtained from several successive "steps" of the curve.
Holt has also modified the Stewart-Hamilton flow formula in order to calculate $V_s$ directly from the discontinuous dilution curve. If $V_s$ and $F$ are constant over the period of measurement, then it is easy to show that

$$V_s = \frac{m_i}{n} \sum_{i=1}^{n} C_i$$  \hspace{1cm} (56)

where $C_0 = 0$.

If the discontinuities of equation (53) are smoothed out by mixing in the exit flow channel, then it is a fair assumption that the concentration in that channel near the ventricular exit, $C(t)$, will be given for all values of $t$ by

$$C(t) = C_1 \left(\frac{V_s}{V_a}\right)^{Q/V_s} = C_1 \left(\frac{V_s}{V_a + V_r}\right)^{(Q/V_s)t}$$  \hspace{1cm} (57)

Since this is an exponential, log $C(t)$ will be a linear function of $t$:

$$\log C(t) = \log C_1 + \frac{Q}{V_s} \log \left(\frac{V_r}{V_a + V_r}\right) .$$  \hspace{1cm} (58)

The slope of the semilogarithmic plot of (58) is thus $\frac{Q}{V_s} \log \frac{V_r}{V_a + V_r}$. Having determined this slope as well as $Q$ and $V_s$ experimentally, we can calculate $V_r$ and thus $V_a$. This method was suggested by Newman and associates.8

Finally we note that if we are interested in the average behavior of the ventricle as a virtual constant-volume mixing chamber, we can write equation (57) as

$$C(t) = C_1 e^{\ln(V_a/V_r) \frac{(Q/V_s)t}{\ln(V_a/V_r)}} = C_1 e^{\ln(V_a/V_r) - (Q/V) t}$$  \hspace{1cm} (59)

where $V = \frac{V_a - V_r}{\ln(V_a/V_r)}$. Thus the ventricle can be treated as a mixing chamber of constant volume, $V$.28 This virtual volume is somewhere between $V_a$ and $V_r$, but not simply their arithmetic mean.

How closely does the behavior of the physiologic prototype approach the theoretical model, and how valid are estimates of ventricular volumes made by these methods?

*Discontinuous exponential* (equation 53).

Not unexpectedly, evidence is beginning to accumulate that correspondence between model and prototype is not nearly as close as we would like. Excluding distortions introduced by the monitoring system, which have been progressively reduced since the early effort of Bing and associates, the major difficulty involves less than ideal ventricular mixing. Thus, samples drawn simultaneously from two different sites within the ventricle rarely showed equal concentration of indicator and frequently the differences were quite large.20 There is also evidence that blood entering the ventricle during dias-
tole does not mix well with the residual blood, and that this indicator-poor fraction is discharged early in systole.20,31 These find-

ings do not necessarily mean that the method is useless. They do mean that careful studies are required to define the limits, if any, within which the procedure can be used with confidence. We expect that such studies will continue to appear.

In this connection, it is profitable to examine more closely the necessary and sufficient conditions for the valid use of equations (55) and (56) in the calculation of ventricular...
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volumes. We shall continue to assume a steady-state cycle with constant $F$, $V_a$, $V_d$, and $V_r$. The equations are of course valid for instantaneous homogeneous mixing. But Holt\cite{Holt} has pointed out that equation (56) is valid even though this condition is violated.

It is only necessary that the sum determined in the aorta be equal to the sum of the average concentrations in the strokes ejected during the determination and that when $C_a = 0$, all indicator has left the ventricle, that is, that no indicator be irreversibly sequestered in the ventricle. Holt has pointed out that the validity of equation (55) does not depend upon the assumption of homogeneous mixing in the ventricle at the end of each diastole. It is only required that the average ratio, $\frac{C_n}{C_{n-1}}$, calculated from the aortic curve be equal to the corresponding average ratio, $\left(\frac{C_n}{C_{n-1}}\right) V_d$, representing the average concentration of the indicator in all of the blood in the ventricle at the end of successive diastoles. Thus we note that the nonhomogeneous ventricular mixing reported by several authors\cite{Kinman, Moore, Hamilton, Kinman, Spurling} cannot in itself invalidate the method.

Summary

In this paper, we have considered some of the basic concepts underlying the measurement of vascular volumes by indicator-dilution methods. Granting the assumptions of stationary flow and homogeneous labeling of flowing blood, the classical Stewart-Hamilton prescription, $V = Q$, provides a valid estimate of central volume. Although the boundaries of this volume can be precisely defined in terms of "time distances," the anatomic description is less definite. The classical treatment did not provide a theoretical model from which the form of the indicator-dilution curve could be deduced but a number of such models have now appeared. These include the mixing-chamber model of Newman and the stochastic models of Sheppard. The slope-volume based on Newman's model measures some fraction of the classical central volume, but precise anatomic boundaries probably cannot be assigned to it. We have attempted to show that so long as we deal with a linear system, the indicator-dilution problem, including recirculation, can be conveniently treated in terms of a block diagram-transfer function approach. Finally we have considered some of the theoretical and practical aspects of the measurement of ventricular volumes.

In conclusion, it might be appropriate to say something about mathematical models in general. Every such model is an abstraction which deliberately neglects certain features of the prototype in order to make possible the rigorous treatment of others. We should therefore not be disappointed to find that "no thoroughly defined system can be expected to mimic completely all of the phenomena of physiological importance." What we should demand of a model is that it mimic enough of these phenomena to make it useful, and that it point the way to its own continuing improvement. If it does these things, it cannot help but be a contribution to the advancement of both theory and practice.

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