Some Theoretical Aspects of Quantification of Mitral Valve Regurgitation by the Indicator-Dilution Method

Sufficient and Insufficient Experiments

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Indicator-dilution curves have been used in the past for the determination of cardiac output, measurement of so-called cardiopulmonary or central blood volume, detection of intracardiac shunts, and, more recently, in an attempt to quantify valvular insufficiency. Despite the extensive literature which has accumulated and which has been recently reviewed by Dow, a complete, theoretical analysis of the indicator output from a two-chamber pulsatile heart is lacking. Analysis of a more simple system, namely, a single pulsatile chamber, has been made by Newman et al. and Holt.

To meet this need for an analysis of the indicator output of a two-chamber pulsatile heart, both in the presence and absence of valvular regurgitation, we have undertaken to study the behavior of a mathematical model simulating action of the heart. At a time when this work was almost complete, McClure, Lacy, Latimer, and Newman published a partial analysis of the performance of a similar model. Although the overall conclusions were generally the same, there were certain dissimilarities in the method of approach between the development published by these authors and our own study. Furthermore, our more complete analysis has led us to certain striking conclusions regarding the use of indicator-dilution curves for quantifying regurgitation.

Methods

Anatomical Parameter of the Mathematical Model

In our model, the anatomical characteristics of a heart (right or left) are defined by four volumes. The following notation will be used:

- General: \((V_a)\); \((V_{v,r}/V_b; F)\); \(L\).
- Special case: \((400); (110/30; 70); L = 0.30\).

The volume in the first set of parentheses defines the atrium; the three volumes in the second set define the ventricle:

Illustrative heart

- \(V_a\) — Maximum volume of the atrium 400 cc.
- \(V_{v,r}\) — Residual (end-systolic) volume of the ventricle 110 cc.
- \(V_b\) — Volume of back flow per stroke 30 cc.
- \(F\) — Net forward ventricular output per stroke 70 cc.

In addition, two other quantities require definition:

- \(V_v\) — Maximum (end-diastolic) volume of the ventricle 210 cc.
- \(L\) — Fraction of ventricular output returning to atrium 0.30.

To simplify the equations which follow, the following dimensionless ratios are defined:

Special case \((400); (110/30; 70)\)

- \(g = (V_b + F)/V_a = \) Ratio of total ventricular stroke to atrial volume 100/400.
- \(b = V_{v,r}/V_v = \) Residual ventricular volume expressed as a fraction of the maximum ventricular volume 110/210.
- \(c = (V_b + F)/V_v = \) Total ventricular stroke expressed as a fraction of the maximum ventricular volume 100/210.
The behavior of heart model I during a complete cycle will be described, again using as an illustration the special case: (400); (110/30; 70). Zero time was chosen arbitrarily as the instant when the atrial volume is at its maximum and the ventricular volume is at its minimum. Thus, at the beginning of the cycle, the atrial volume is 400 cc.; the ventricular volume is 110 cc. During the cycle the atrium delivers 100 cc. of blood to the ventricle; the atrial volume drops to 300 cc.; the ventricular volume increases to 210 cc. The ventricle contracts, sending 30 cc. back into the atrium and 70 cc. forward into the artery. At the same time, the vein delivers 70 cc. of blood to the atrium. The cycle is now complete.

In model I, the movements of blood from atrium to ventricle and from vein to atrium are consecutive, not concurrent, during a given cycle. Delivery of blood from vein to atrium does not begin until after the ventricle receives its full quota of blood. In model II, the movements of blood from vein to atrium and from atrium to ventricle take place concurrently.

**Functional Description of Model II**

At zero time the atrial and ventricular volumes are 400 and 110 cc., as in model I. During the cycle, the vein delivers blood to the atrium at a constant rate. At the same time, the atrium delivers blood to the ventricle, also at a constant, but not necessarily the same rate. By the time the movement of blood is completed, the atrium has received 70 cc. from the vein and delivered 100 cc. to the ventricle. The volume of the atrium drops to 370 cc. (in model I, the minimum volume is 300 cc.). The volume of the ventricle increases to 210 cc. (as in model I).

Toward the end of the cycle, the ventricle contracts to 110 cc., sending 30 cc. back into the atrium and 70 cc. forward into the artery. The cycle is now complete.

Aside from the fact that the minimum atrial volumes are different in the two models, they differ in the amount of indicator delivered per stroke from atrium to ventricle. In model II, the blood coming in from the vein dilutes the indicator in the atrium. Thus, even though the ventricle receives the same volume of blood in both models, in model II, the ventricle receives a smaller fraction of the atrium indicator than it does in model I.

We have investigated the theoretical indicator-dilution curves obtained from both models. There is no qualitative difference in the appearances of the curves. When the atrium is large, around 400 cc., the quantitative differences are relatively small. The differences increase as the atrium is made progressively smaller.

The mathematics of model II are much more cumbersome than those of model I. Our primary interest was directed toward quantification of atrioventricular valve regurgitation. This regurgitation is usually associated with enlargement of the atrium. With large atria the quantitative differences between the two models are small. For these reasons the present report is confined to an analysis of model I.

**Difference Equations**

In the analysis of a system with continuous flow, one starts with a system of differential equations which define the changes in the variables with time. When the flow is discontinuous, as in the case in a pulsating heart, it is necessary to start with a system of difference equations. The end product consists of equations which give the values of the variables at the end (or start) of each cycle.

Since the experimental quantities usually encountered are concentrations and not amounts of indicator present in each compartment, we chose concentrations as our main variables. We will assume that sampling may be carried out in the atrium, in the ventricle, and in the artery just outside the ventricle and that mixing is complete.

The symbols $a_i$, $v_i$, $p_i$ represent the indicator concentrations in the atrium, in the ventricle, and in the artery just outside the ventricle at the end of the $i$-th cycle. An instantaneous injection of the indicator is carried out at the start of a cycle, and the count of cycles begins. We define $a_0$, $v_0$, $p_0$ as the concentrations at the start of the first cycle immediately after the instantaneous injection of the dye. Thus, if a dose of I units of the indicator is in-
MITRAL REGURGITATION

jected in the atrium: \( a_o = I/V_a; v_o = P_a = 0 \). On the other hand, if the injection is ventricular, then: \( v_o = I/V_v; a_o = P_v = 0 \).

It should be pointed out that, beginning with the end of the first cycle, \( p_i = v_i \). For this reason, \( a_i \) and \( v_i \) were chosen as the variables; the dependence of these variables on \( i \) is to be investigated.

The following pair of simultaneous difference equations yields the values of the two concentrations at the end of some particular cycle in terms of the concentrations at the end of the preceding cycle. The derivation of these equations is given in Appendix 1.

\[
\begin{align*}
v_{i+1} = c a_i + b v_i; \quad (2) \\
a_{i+1} = r a_i + g L b v_i; \quad (r = 1 - g + g L c). \quad (3)
\end{align*}
\]

For a given heart, different injection and sampling sites will yield different sequences. The initial concentrations depend on the manner and site of injection. However, once the injection is complete, different as the curves may be from one experiment to another, a given experiment will yield two sets of concentration sequences, each of which satisfies the respective difference equation. In other words, the anatomical parameters and the difference equations are characteristics of the individual heart. On the other hand, the sequences obtained depend not only on the specific heart but also on the manner in which the experiment is started.

Elementary Experiments

An experiment with the mathematical model may be carried out in a multitude of ways: The indicator may be injected into a single compartment or simultaneously into two compartments. Sampling may be carried out at one or more sites. Other variations easily suggest themselves. We found it most profitable to examine the behavior of the model in elementary experiments, i.e., experiments in which there is a single instantaneous injection into one of the chambers and sampling at one site only.

Using the letters \( A, V, \) and \( P \) for the adjectives "atrial," "ventricular," and "peripheral," respectively, an elementary experiment will be described by two letters: \( A-A; A-V; A-P; V-A; V-V; V-P \). The first letter defines the site of injection; the second letter defines the sampling site. The term peripheral is defined throughout to mean a location just outside the ventricle, i.e., the base of the aorta.

In a clinical elementary experiment the investigator obtains a single curve only. In a mathematical experiment one automatically obtains both the sequences of atrial and of ventricular concentrations.

Results

Atrial Injection Experiments

As an illustration of a mathematical experiment with the model, we present the results of an atrial injection into the following heart:

\[
(420); \quad (84/14; 70); \quad L = 1/6. \quad (420);
\]

\[
b = 0.50; \quad g = 0.20; \quad g L b = g L e = 0.0166667; \quad r = 1 - g + g L e = 0.816667. \quad (70);
\]

In order to evaluate the errors involved in certain approximations discussed later, the calculations were originally carried out to six significant figures. Substitution of the above values into the general formulas for the difference equations 2 and 3 yields the difference equations for this particular heart:

\[
a_{i+1} = 0.816667 a_i + 0.016667 v_i. \quad (4)
\]

\[
v_{i+1} = 0.5 a_i + 0.5 v_i. \quad (5)
\]

For an atrial injection of 1 unit of indicator, the initial concentrations are as follows:

\[
a_o = 1/0.420 = 2.380952 \text{ I units of indicator per liter} \quad v_o = 0. \quad (6)
\]

The calculated V-A and V-V sequences are also shown in figure 1. With the exception of

Circulation Research, Volume IX, May 1961
Figure 1
Concentration sequences obtained from the heart, the specifications of which are given in the figure. The points show concentrations at the end of each beat. (Left panel): atrial injection at zero time. Ventricular (and peripheral) concentrations are represented by the A-V curve; atrial concentrations by the A-A curve. (Right panel): ventricular injection at zero time. Ventricular (and peripheral) concentrations are represented by the V-V curve; atrial concentrations by the V-A curve. Each of the four sequences approaches a linear phase. The slopes of all four linear phases (the downstroke slopes) are the same. In each pair of sequences the ratio \( v_i/a_i \) approaches the same value \( K \). The V-A sequence has precisely the same shape as the A-V sequence. The concentrations at each value of \( i \) are in the ratio \( L \).

the value at zero time, the V-P sequence is the same as the V-V sequence. The zero value of \( P_1 \) is zero.

Values of the Limiting Ratios: \( a_{i+i}/a_i = v_{i+i}/v_i = R \) and \( v_i/a_i = K \)

Inspection of the four sequences shown in figure 1 reveals that they possess the following interesting characteristics:

1. Each of the four curves approaches linearity for large enough values of \( i \). This means that the ratio of two consecutive concentrations approaches a constant limit.

2. The slopes of all four curves approach the same value:

\[
\text{Lim. } (a_{i+1}/a_i) = \text{lim. } (v_{i+1}/v_i) = R \quad \text{(definition of } R)\]

3. The vertical separation between the linear branches of the two curves in each pair is the same. This means that for a given heart, no matter what type of injection is used, the following equation holds:

\[
\text{Lim. } (v_i/a_i) = K \quad \text{(definition of } K)\]

It is worth emphasizing that both \( R \) and \( K \) are characteristics of the heart and are independent of the manner in which the experiment is started.

Given the specifications of a heart, a single mathematical run carried out to a large enough value of \( i \) will disclose the values of both \( R \) and \( K \) for the heart in question. However, these two quantities can be calculated in advance with the use of the following two formulas, developed in Appendix 2:

\[
R = \frac{1}{2} \left( \frac{r+b}{r-b} + \sqrt{(r-b)^2 + 4gLbc} \right) \quad \text{(10)}
\]

\[
K = \frac{\sqrt{(r-b)^2 + 4gLbc} - (r-b)}{2gLb} = \frac{c}{R-b} \quad \text{(11)}
\]

Equation 10 offers a powerful tool for the examination of the dependence of the ultimate downstroke slope on individual parameters of the heart or on a pair of parameters, varied jointly according to some specified rule. Before presenting the results of this type of systematic analysis, it will be necessary to select a convenient unit of time and to discuss the relation between the values of \( R \) and the downstroke slope.

Relation Between the Value of \( R \) and the Downstroke Slope

In a theoretical analysis of the function of the heart, formulas are simpler when the natural time-unit of the heart, the heartbeat, is taken as the unit of time. For this reason the slope of a curve is defined as the change of the logarithm of the concentration per beat:

\[
\text{Slope} = \frac{\text{Log } C_{i+1} - \text{Log } C_i}{(i+1) - i} = \text{Log} \left( \frac{C_{i+1}}{C_i} \right) = \text{Log } R \quad \text{(per beat)} = s. \quad \text{(12)}
\]

Effects of the Various Heart Parameters on the Downstroke Slope

One of our immediate objectives was to develop a quantitative measure of the extent of regurgitation in terms of the parameters of the heart. In particular, we wished to test the hypothesis of Korner and Shillingford\(^{12}\) that the extent of regurgitation may be quantified in terms of the measured downstroke slope.

* Circulation Research, Volume IX, May 1961*
As was mentioned earlier, the downstroke slope, expressed in logarithmic units per beat, equals Log R. Any desired information about the functional relation between the downstroke slope and the various parameters is contained in the equation for R (equation 10).

Since the right side of this equation is a function of four independent variables, it would take a surface in a five-dimensional space to represent graphically the dependence of the downstroke slope on all the parameters. For this reason, it is necessary to examine piece-meal the dependence of the slope on each individual parameter.

The functional relations are simplest in a nonregurgitant heart. In an A-A experiment, the concentration sequence is an exponential decay function, with \( R = 1 - g \). In V-V or V-P experiments the concentration sequence is also a simple exponential decay function, with \( R = 1 - c = b \). With A-V or A-P runs, the concentration sequences are more complex. However, the ultimate value of the ratio of two successive concentrations, \( R \), equals \( 1 - g \), if the maximum volume of the atrium is larger than the maximum ventricular volume. The value of \( R \) is \( b \) if the reverse is true. This is in agreement with Newman's conclusion \(^{19} \) that in a model with continuous flow, the reservoir with the largest volume determines the ultimate downstroke slope. Thus, this rule also holds true in a system containing pulsating volumes but without regurgitation.

In order to present graphically the influence of each of the parameters on the downstroke slope, it is convenient to choose some particular heart and to show the relative change in the downstroke slopes when one of the parameters, \( p \), is changed. Let \( s^* \) and \( p^* \) be, respectively, the values of the slope and of the parameter under consideration for the particular heart chosen as "standard." A plot of \( s/s^* \) vs \( p/p^* \) results in curves for the various parameters which all pass through the same point, namely, \( p/p^* = 1 \); \( s/s^* = 1 \). The slope of the curve at or near the standard heart will be referred to as the sensitivity of the downstroke slope to the parameter under examination.

Figure 2 shows the relation between the downstroke slope and several parameters of a nonregurgitant heart. The following heart was chosen as "standard": \((175); (70/70); L = 0; R^* = 0.600; s^* = -0.2285 per beat. In each panel, the abscissa represents the relative value of the parameter under examination; the ordinate represents the relative value of the downstroke slope. Each curve as a whole represents a series of hearts generated by changing the independent parameter. In each panel, the large open circle represents the "standard" heart.

In each diagram, except panel V, the curve representing the series of hearts consists of two parts. In one part (solid curve), the
maximum volume of the atrium is larger than the maximum volume of the ventricle, and the downstroke slope is determined solely by the size of the atrium. In the second part of the series (broken curve), the ventricle is larger than the atrium, and the downstroke is controlled solely by the ventricle. The two branches meet at a cusp indicated by two concentric circles. The cusp represents the member of the series of hearts whose atrium and ventricle are of equal volume. In this particular heart the atrium and ventricle both demand the same downstroke slope. Attention is called to the fact that, in the ideal mathematical model, control of the downstroke slope passes abruptly from one chamber to the other.

Panel I shows the effect of the residual volume on the downstroke slope. In the neighborhood of the "standard" heart, the slope is controlled solely by the atrium and is independent of the residual volume. At the cusp, \( V_r = 105 \text{ cc.} \); \( V_a = V_v = 175 \text{ cc.} \). Beyond the cusp, the slope is controlled by the ventricle. As the ventricle increases, the slope diminishes.

Panel II shows the effect of changing both the residual ventricular volume and the atrium, but in such a way that the sum of these two volumes is kept constant at 245 cc. Since \( s/s^* \) is plotted against \( V_r/V_v, r^*, \) the ventricle increases as the point moves toward the right, whereas the atrium decreases. At first, the atrium exercises sole control over the slope. As the atrium decreases, the slope increases. The cusp occurs at \( V_v, r = 87.5 \text{ cc.} \); \( V_v = V_a = 157.5 \text{ cc.} \). At the cusp, the ventricle takes over control over the slope. As the ventricle continues to increase, the slope decreases.

Panel III shows the effect of the atrial volume on the slope. As the atrium decreases between the "standard" heart and the cusp, the slope increases up to the cusp. At the cusp, \( V_a = V_v = 140 \text{ cc.} \). To the left of the cusp, the ventricle is larger than the atrium and exercises sole control over the slope. Since the volume of the ventricle is kept constant, the slope remains constant.

Panel IV shows the effect on the slope of the cardiac output per beat. The atrial volume remains constant in this series of hearts, but the ventricular volume increases with the cardiac output. At first, the atrium is larger than the ventricle and exercises sole control over the slope. With a constant atrium and increasing stroke, the slope increases. The cusp is reached when \( F = 105 \text{ cc.} \); \( V_v = V_a = 175 \text{ cc.} \). Beyond the cusp, control over the slope is taken over by the ventricle. The slope continues to increase but at a smaller rate.

Panel V shows the relation between the downstroke slope and frequency of the heart beat. Given a "standard" heart, the slope expressed in logarithmic units per heart beat is independent of the frequency. However, when the slope is expressed, as is common, in logarithmic units per second, the downstroke slope is directly proportional to the frequency.

The series of hearts represented in panel II of figure 2 are of particular interest. Every member of this series produces the same output per beat and possesses the same total volume. They differ from each other in the relative volumes of the atrium and the ventricle. The graph shows that the downstroke slope is not constant for the series. This observation contradicts the assumption underlying the method of quantifying regurgitation proposed by Korner and Shillingford. These investigators obtained a variety of indicator-dilution curves from a large sample of non-regurgitant human hearts. For each experimental curve, the respective values of the cardiac output, the needle-to-needle (central) volume, and the downstroke slope are calculated. A regression equation is obtained, expressing the downstroke slope as a function of the cardiac output and the needle-to-needle volume. Having established a norm for non-regurgitant hearts, Korner and Shillingford assume that deviation from this norm may be used as a measure of regurgitation.

The setting of the norm for the slope is based on the tacit assumption that for non-regurgitant hearts the downstroke slope may be predicted from two parameters of the system. As was pointed out earlier, the down-
stroke slope in a normal heart may be controlled either by the atrium or by the ventricle, whichever is larger. Furthermore, the graph in panel II of figure 2 shows that in a series of hearts with constant cardiac output and constant cardiac volume, the slope is not constant.

The dependence of the downstroke slope of curves from regurgitant hearts on various parameters is much more complicated than is the case for nonregurgitant hearts. No longer does the larger of the two compartments exercise sole control over the slope. Control is shared by both compartments. Because of the joint control, there is no sudden transition, and each curve is a smooth analytical function. Despite the complexity of equation 10, the following rules hold: If the atrium is much larger than the ventricle, the downstroke slope is approximately equal to Log (1 - g) but somewhat smaller. If the ventricle is much larger than the atrium, the downstroke slope is approximately equal to Log b but somewhat smaller. The smaller the amount of regurgitation, the more accurate are these rules.

Figure 3 shows the relation between s/s* and various parameters for a regurgitant heart. The following heart was chosen as "standard" in all cases: (400); (140/70; 70); L* = 0.50; R* = 0.859 28; s* = 0.065 87 Log units per beat. Again, in each panel the "standard" heart is represented by a circle. In plotting the solid curves, the same scale was used for both coordinates. Since in panels I to III the slopes of the curves near the "standard" heart are rather small, a section of the solid curve near the central point was plotted with a 10-fold magnification of the ordinate scale and was plotted as a broken curve. The scales for the broken curves are shown to the right of panels I to III.

Panel I shows the dependence of the downstroke slope on the volume regurgitating per beat. The solid curve, with equal vertical and horizontal scales, shows the lack of sensitivity of the downstroke slope to the retrograde volume. The sensitivity of the downstroke slope near the central point equals the slope of the solid curve at this point and is 0.08. This means that for small changes in the retrograde volume, the per cent change in the downstroke slope is only 0.08 times as large as the per cent change in the retrograde volume. For larger relative changes, the relative change in the downstroke slope is different. Thus, when the retrograde volume is changed to one half of the "standard" retrograde volume, the downstroke slope increases by only 6 per cent. When the retrograde volume is greater by a factor of 1.5, the downstroke slope is smaller by only 3 per cent.

Panel II shows the sensitivity of the downstroke slope to the residual ventricular volume. The sensitivity near the central point is 0.234; that is, for small, relative changes the relative change in the slope is a little less than one quarter the relative change in the residual volume.

Panel V, curve V_a, shows the sensitivity of
the slope to the atrial volume. The sensitivity near the central point is 0.84.

Panel III shows the change in the downstroke when both the ventricular and atrial volumes are changed, but in such a manner as to keep the sum of the two volumes constant. The curve is plotted against values of $V_v, r/V_v, r^*$. Therefore, as the abscissa increases, the ventricle increases, and the atrium decreases. A decrease in the atrium tends to increase the slope, and increase of the ventricle tends to decrease the slope. Near the central point the first effect predominates, and the curve has a positive slope. When the residual volume of the ventricle is 200 cc, then $V_v, r/V_v, r^* = 1.429$, the total volume of the ventricle is 340 cc, and the atrial volume is also 340 cc. At this point the two effects balance each other, and the curve passes through a maximum. Beyond this point the effect of the increasing ventricle predominates, and the slope of the curve is negative.

As may be seen, however, the sensitivity in the entire series is poor.

Panel IV shows the sensitivity of the downstroke slope to the net cardiac output per beat, $F$. As may be seen, the downstroke slope is most sensitive to this parameter. The sensitivity at the central point is 1.12.

Panel V, curve f, shows the sensitivity of the downstroke slope to the frequency of heartbeat when the slope is measured in logarithmic units per second. The sensitivity of the slope is exactly 1.

In summary, figure 3 demonstrates the extreme lack of sensitivity of the downstroke slope to the value of the retrograde volume. It follows that at best the downstroke slope is a rather insensitive index of the extent of regurgitation. It is obvious, therefore, that in order to quantify regurgitation, it is necessary to examine the indicator-dilution curve as a whole by an examination of the solution of the pair of difference equations.

Solution of the Difference Equations

The process of solving the pair of difference equations 2 and 3 consists of a standard, if not widely familiar, procedure. It is lengthy and cumbersome, and for this reason the complete derivation is omitted. The solutions for each of the two kinds of injection are given in the equations which follow.

First, certain symbols representing combinations of the parameters of the heart are defined. The solutions of the difference equations are then given in terms of these quantities. Symbols used in the solutions are:

\[
\begin{align*}
    r &= 1 - g + gLe. \\
    \sqrt{r} &= \sqrt{(r-b)^2 + 4gLbc}. \\
    M &= \frac{1}{2} [\sqrt{r} + (r-b)]. \\
    M' &= \frac{1}{2} [\sqrt{r} - (r-b)]. \\
    R &= \frac{1}{2} [(r+b) + \sqrt{r}]. \\
    R' &= \frac{1}{2} [(r+b) - \sqrt{r}].
\end{align*}
\]

Atrial Injection of Dose I:

\[
\begin{align*}
    A-A \text{ sequence: } a_1 &= \frac{I r M}{V_v, r} R^1 + \frac{I r M'}{V_v, r} R^1. \\
    A-V \text{ sequence: } v_1 &= \frac{I e}{V_v, r} R^1 - \frac{I e}{V_v, r} R^1.
\end{align*}
\]

Ventricular Injection of Dose I:

\[
\begin{align*}
    V-A \text{ sequence: } a_1 &= \frac{I r g L}{V_v, r} R^1 - \frac{I r g L}{V_v, r} R^1. \\
    V-V \text{ sequence: } v_1 &= \frac{I r M'}{b V_v, r} R^1 + \frac{I r M}{b V_v, r} R^1.
\end{align*}
\]

Sequence Sums and Relation to the Forward Flow, $F$

In a system with continuous, constant flow, a smooth concentration curve, $C(t)$, is obtained. The volume-rate of flow, or net cardiac output, $Q$, is obtained by the use of the well-known Stewart-Hamilton equation:

\[
Q = \int C(t) \, dt
\]

In our model, the concentration is not a continuous but a stepwise function $C_t$, where $C_t$ may be $a_t$, $v_t$, or $p_t$. The width of each step is $T_e$, the duration of a cardiac cycle. The rate of flow is not constant, but the mean rate is $\bar{Q} = F/T_e$. Since the integral in the denominator of equation 23 represents the area under the curve, and the area under a stepwise curve, of constant step width $T_e$, equals the expression $T_e \Sigma C_t$, it is necessary to test
whether the following equation is satisfied by
the sequences obtained in the four elementary
experiments defined earlier and represented
by equations 19 to 22.

\[ Q = \frac{I}{T_{s} C_{1}} \text{ ; } \sum_{s} C_{1} = \frac{I}{Q T_{e}} \] (24)

In particular, it is desirable to determine
whether this equation is satisfied both by
nonregurgitant and by regurgitant hearts.
Since \( Q T_{e} = F \), the test may be carried out
by determining whether the following equation
is satisfied by the four elementary se-
quences:

\[ \sum_{s} C_{1} = \frac{I}{F} \] (25)

Each of the four sequences defined by equa-
tions 19 to 22 represents the sum or the differ-
ence of two geometric series. On carrying out
the summations to infinity and simplifying
the formulas, the following equations are
obtained:

- **A-A sequence**: \( a_{1} = X_{1} R^{i} + X_{2} R^{-i} \) . (30)
- **A-V sequence**: \( v_{i} = X_{3} R^{i} - X_{3} R^{-i} \) . (31)
- **V-A sequence**: \( a_{i} = X_{4} R^{i} - X_{4} R^{-i} \) . (32)
- **V-V sequence**: \( v_{i} = X_{5} R^{i} + X_{6} R^{-i} \) . (33)

Equations 26 and 27 show that the condition
specified by equation 25 is satisfied by
both the A-A and the A-V sequences. It fol-
ows that the value of the net cardiac output
per beat may be determined either by atrial
injection-atrial sampling or by atrial injec-
tion-ventricular sampling. Equation 29 shows
that the condition specified in equation 25 is
satisfied, provided the value of \( v_{e} \) is not
included in the summation. Finally, from equa-
tion 28 it may be seen that a V-A sequence
cannot give the value for net forward flow
without knowledge of \( L \).

The sums of the sequence in A-A, A-V, and
V-V curves equal the value \( I/F \). They are
not affected by the value of \( L \). For this reason,
the sum of concentrations taken by itself will
not yield any information about the magni-
tude of the leak. The results are different in a
V-A experiment. According to equation 28,
the sum of the observed sequence is \( L/I/F \). It
follows that the value of \( L \) may be obtained
by carrying out a ventricular injection and
by sampling both from the atrium and per-
ipherally. The ratio of the sum of the V-A
sequence to the sum of the V-P sequence will
be equal to \( L \). This suggestion has been pre-
viously offered by Conn et al.\(^{22} \) and by Lacy
et al.\(^{23} \)

**Asymptotic Formulas**

The four elementary sequences represented
by equations 19 to 22 may be written in
simpler form as follows:

- **A-A sequence**: \( a_{i} = X_{1} R^{i} + X_{2} R^{-i} \) . (30)
- **A-V sequence**: \( v_{i} = X_{3} R^{i} - X_{3} R^{-i} \) . (31)
- **V-A sequence**: \( a_{i} = X_{4} R^{i} - X_{4} R^{-i} \) . (32)
- **V-V sequence**: \( v_{i} = X_{5} R^{i} + X_{6} R^{-i} \) . (33)

For a given heart, \( X_{1}, X_{2}, X_{3}, X_{4}, X_{5}, X_{6} \)
are constants expressed in terms of the
parameters of the heart. The formulas for
each of the six constants may be obtained by
comparing each of the four equations with
the respective equations 19 to 22.

Since \( R' \) is smaller than \( R \), it follows that
for high enough values of \( i \), equations 30 to 33
may be approximated by asymptotic equa-
tion 34.

\[ a_{i} = X_{1} R^{i} ; \quad v_{i} = X_{3} R^{i} ; \] (respectively). (34)

In an actual experiment, there is some value
of \( i \) beyond which the difference between the
actual and asymptotic form is smaller than
the experimental analytical error. For brevity
the part of the sequence beyond this point
will be referred to as the "exponential phase."

When the exponential phase is reached, the
ratio of two successive concentrations remains
constant. Inspection of equation 34 will show
that the ratio is the same in all four sequences,

\[ C_{i+1}/C_{i} = \text{constant} = R. \] (35)

This conclusion was reached earlier, directly
from an analysis of the difference equations and without the use of the solution of the difference equations (equation 10, equation $A - 2.07$).

For a given injection (atrial or ventricular), the ratio $v_i/a_i$ becomes constant in the exponential phase. This may be seen by comparing pairwise the asymptotic forms of equations 19 and 20 and of equations 21 and 22:

Atrial injection:

$$\frac{v_i}{a_i} = \frac{c}{M} \quad \text{(exponential phase only).}$$  
(36)

Ventricular injection:

$$\frac{v_i}{a_i} = \frac{M'}{gLb} \quad \text{(exponential phase only).}$$  
(37)

The values of the two ratios are different in form only. Substitution of the values of $M$ and of $M'$, as given in equations 15 and 16, will show that the two ratios are identical:

$$\frac{v_i}{a_i} = \frac{c}{M} \quad \text{(exponential phase only).}$$  
(38)

The conclusion obtained previously directly from the difference equations is verified, namely, that in the presence of regurgitation, the ratio $v_i/a_i$ approaches the constant value $K$ independently of whether the injection is atrial or ventricular.

The equations and formulas given in equations 13 to 22 are valid for any regurgitant heart. For nonregurgitant hearts ($L = 0$), the formulas are simpler.

Formulas for Nonregurgitant Hearts

The formulas which follow are applicable to nonregurgitant hearts.

Atrial Injection of Dose I

A-A sequence:

$$a_i = \frac{I}{V_a} (1-g)^i ; \quad R = 1-g .$$  
(39)

A-V sequence:

Atrium is larger than ventricle

$$(V_a > V_b ; 1-g > b ; c > g)$$

$$v_i = \frac{I}{V_a} (1-g)^i \quad \text{or } \frac{c}{e-g} \quad \{b^i - (1-g)^i \} ; \quad R = b ; \quad K = \infty .$$  
(40)

Atrium is same size as ventricle

$$(1-g = b ; c = g)$$

$$v_i = \frac{I}{V_a} b^i ; \quad R = b ; \quad K = \infty .$$  
(41)

Ventricular Injection of Dose I

V-A sequence:

$$a_i = 0 \quad \text{(for all values of } i) .$$  
(43)

V-V sequence:

$$v_i = \frac{I}{bV_v} b^i ; \quad R = b ; \quad K = \infty .$$  
(44)

The formula for an A-V sequence, as well as equations 39 to 44, may be obtained from the general equations 19 to 22 by substitution of the value $L = 0$. However, the structure of the formula for the A-V sequence depends on the relative sizes of the atrium and the ventricle (equations 40 to 42). The reason for this is given in Appendix 3.

Because of the eventual appearance of recirculation, it is customary to evaluate the integrals appearing in equations 23 and 24 from the values of the concentrations just before the appearance of recirculation and from the slope of the curve on a semilog plot. For this reason, the rate of approach to the ultimate slope is of some practical interest. As may be seen from equations 40 and 42, the rate of approach is dependent on the disparity between the values of $(1-g)$ and of $b$. The smaller the disparity, the slower is the rate of approach and the larger the discrepancy between the last observed value of the slope and the theoretical ultimate value.

The rate of approach to the ultimate slope is smallest when the two compartments are of equal size. As may be seen from equation 41, the value of $v_i \cdot i/v_i$ is $b(i+1)/i$. Thus, if recirculation begins to assert itself after the eleventh beat, the observed ratio of the two last successive concentrations is $b(11/10) = 1.1b$ and is 10 per cent larger than the theoretical ultimate value $b$.

Calculation of the Parameters of the Heart from a V-V Sequence

It is now possible to turn to the main object of our investigation, namely, given the data obtained from a single indicator-dilution
experiment, calculate the parameters of the heart and, particularly, the extent of atrio-
ventricular valve regurgitation. The theoretical analysis of a V-V sequence will be taken
up first.

Assume that on carrying out a V-V experiment, the numerical values are obtained for a
finite number of terms of the sequence \( v_i \). By comparison with equation 33, the theoretical
expression for the sequence may be written as the sum of two exponential functions:

\[
v_i \text{ (known)} = v_i^* + v_i^{**} \quad (45)
\]

where \( v_i^* = X_5 R' \); \( v_i^{**} = X_6 R'^4 \) \( (46) \)

and \( X_5, R, X_6, R' \) are known functions of the parameters of the heart. The problem is, first,
to calculate the numerical values of these four quantities from the known values of \( v_i \) and,
next, to use these four quantities in the evaluation of the parameters of the heart.

Since there are four unknowns, it is possible, in principle, to calculate the values of the
unknowns from four values of \( v_i \) by a laborious process of trial and error. In practice, it
is simpler to calculate approximate estimates of the four unknowns by the familiar tech-
nique of separating the sum of two simple exponentials into its two components.

On theoretical grounds, the terms of the sequence \( v_i^{**} \) decrease faster than the terms of \( v_i^* \). As a first approximation, assume that for the last few terms of the known sequence \( v_i \), the values of \( v_i^{**} \) are negligibly small compared with \( v_i^* \). We now have the approximate equation:

\[
X_5 R' = v_i^* = v_i \quad (\text{approximately; last few terms only}) \quad (47)
\]

Using the last few terms, one can calculate estimates of the numerical values of \( R \) out of
\( X_5 \). One can also reconstruct the sequence \( v_i^* \) all the way back to \( v_0^* \). With the sequence \( v_i^* \) known, one can then reconstruct the sequence \( v_i^{**} \):

\[
v_i^{**} = v_i \text{ (known)} - v_i^* \text{ (known)} = X_6 R'^4 \quad (48)
\]

Finally, with the sequence \( v_i^{**} \) known approximately, it is possible to estimate the
numerical values of \( X_6 \) and of \( R' \). With \( R, R', X_5, X_6 \) known, a comparison of equation
33 with equation 22 yields a system of four simultaneous equations:

\[
\frac{1}{b V_v} = \frac{X_5 \text{ (known)}}{ \sqrt{v_i} } \quad (49)
\]

\[
\frac{1}{b V_v} = \frac{X_6 \text{ (known)}}{ \sqrt{v_i} } \quad (50)
\]

\[
R = \text{(known)} \quad (51)
\]

\[
R' = \text{(known)} \quad (52)
\]

The left side of each of the four equations contains the unknowns \( V_v, b, c, L, g \). However,
there are only four independent unknowns since \( b = 1-c \). We are faced with a system of
four equations in four unknowns. Since the number of equations equals the number of
unknowns, a unique solution can be obtained.

Since the four quantities appearing on the right side of the last four equations are ad-
mittedly somewhat in error because of the approximate nature of equation 47, it follows
that errors will be introduced in the solution of the parameters of the heart. A thorough
general analysis of these errors would be entirely too cumbersome. However, it is de-
sirable to form an estimate of the order of magnitude of the errors introduced by the
approximate procedure. We have carried out an experimental mathematical run with the
following heart: \( (420); \ (64/14; 70) \); \( L = 1/6 \); ventricular injection. We stopped with
\( v_{12} \) and used the last two terms of the sequence to define the auxiliary sequence \( v_i^* \) of equa-
tion 47.

The results of our calculations are given in table 1. The various quantities are listed in
the order in which they were obtained. Asterisks mark the quantities usually desired,
namely, the anatomical features of the heart. The last column shows the per cent difference
between the calculated and the true values.

As may be seen, there is a large range of errors, from 0.20 per cent in the evaluation of
\( F \) to 16.2 per cent in the evaluation of \( X_5 \). If we confine our interest to the calculated
values of the anatomical parameters of the heart, the error in the estimated value of \( L \)
is only 3.3 per cent, and the largest error, 6.1
Table 1

Results of the Analysis of the V-V (or V-P) Sequence Obtained from Heart (420); (84/14; 70)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Estimated value</th>
<th>True value</th>
<th>Per cent error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R (cc.)</td>
<td>0.831 66</td>
<td>0.841 10</td>
<td>- 1.12</td>
</tr>
<tr>
<td>2 F (cc.)</td>
<td>70.143</td>
<td>70.000</td>
<td>+ 0.20*</td>
</tr>
<tr>
<td>3 Xx</td>
<td>0.924 57</td>
<td>0.795 65</td>
<td>+16.2</td>
</tr>
<tr>
<td>4 R'</td>
<td>0.471 7</td>
<td>0.475 57</td>
<td>- 0.81</td>
</tr>
<tr>
<td>5 Xx</td>
<td>10.988</td>
<td>11.109</td>
<td>- 1.1</td>
</tr>
<tr>
<td>6 Vv (cc.)</td>
<td>84.60</td>
<td>80.000</td>
<td>+ 0.71*</td>
</tr>
<tr>
<td>7 b</td>
<td>0.499 64</td>
<td>0.500 00</td>
<td>- 0.072</td>
</tr>
<tr>
<td>8 Vv (cc.)</td>
<td>169.32</td>
<td>168.00</td>
<td>+ 0.79*</td>
</tr>
<tr>
<td>9 Regurgitant volume (cc.)</td>
<td>14.58</td>
<td>14.000</td>
<td>+ 4.14*</td>
</tr>
<tr>
<td>10 L</td>
<td>0.172 1</td>
<td>0.166 67</td>
<td>+ 3.3*</td>
</tr>
<tr>
<td>11 Vv (cc.)</td>
<td>394.41</td>
<td>420.00</td>
<td>- 6.1*</td>
</tr>
</tbody>
</table>

*Quantities usually desired, i.e., the anatomical features of the heart.

per cent, occurs in the evaluation of the values of the atrium. The errors in the calculated values are due entirely to the use of the approximate method of segregating the two exponentials and are not too large. Therefore, the considerable effort needed for a more accurate evaluation of the two exponentials is not justifiable.

The above calculations are based on the assumption of immediate, complete mixing after injection. Recent evidence suggests this does not occur within one heartbeat after ventricular injection in vivo. The probable error introduced in a V-V clinical experiment is difficult to assess. One would expect only the initial portion of the sequence to be influenced. In the absence of regurgitation, therefore, little error is likely. The problem in the presence of regurgitation is more complex. To obtain some idea of the magnitude of error which might be produced, we examined the behavior of the heart, (400); (140/70; 70); L = 0.50, in which faulty mixing of indicator occurred after ventricular injection of dose I. We assumed a completely arbitrary distribution of indicator by the end of the first cycle: atrium—0.20 I, ventricle—0.37 I, artery (aorta)—0.43 I. This may be treated mathematically as equivalent to the superposition of three separate injections of 0.43 I into the artery, 0.37 I into the ventricle, and 0.20 I into the atrium. We solved the parameters of the heart from the resultant experimental mathematical run. The derived heart has the volumes (405.1); (137.6/72.6; 70); L = 0.509. The largest error in this case would be 3.7 per cent in the calculation of regurgitant flow per beat (Vb); on the other hand, the error in the calculated value of L (1.8 per cent) is even smaller as a result of partially compensating errors.

Indeterminacy of an A-V Experiment

Assume that an atrial injection—ventricular sampling experiment is carried out. The experiment yields a sequence of known concentrations vi = XxR' - XxR" (equation 31). It is possible to evaluate the quantities Xx, R, and R' by the approximate method outlined in the preceding section.

Comparison of equation 31 with equation 20 yields the following equations:

\[ \frac{I_c}{V_a \cdot \sqrt{g}} = X_x \text{ (known)} \]  \hspace{1cm} (53)

\[ R = \text{ (known)} \]  \hspace{1cm} (54)

\[ R' = \text{ (known)} \]  \hspace{1cm} (55)

The left sides of the three equations contain the unknown Vv, g, L, c. Since there are four unknowns and only three equations, the
solution is indeterminate. In other words, it is possible to find an infinite number of hearts, each differing from the others, which will give the identical A-V sequence v₁. However, since the value of F is determined by the sum of the sequence (equation 27), all the members of the infinite series of hearts have one anatomical parameter in common. They all possess the same net output per beat, F.

Because of the import of our conclusion, the burden is ours to answer the following questions: Is the indeterminacy of the A-V sequence a peculiar feature of our particular model, or is it a characteristic of all possible models of a real heart? If the latter is the case, are there other types of experiments which will yield indeterminate results? Finally, since our models show that the quantity F may be determined even from an indeterminate A-V experiment, is it not possible that the quantity L may also be evaluated, even if the remaining two unknowns are indeterminate? These questions will be taken up in the sections which follow.

Examination of equations 30 to 33 and Appendix 5 yields an answer to one of these questions. If the concentration sampled is that of the reservoir which receives the injection (A-A or V-V), the experimental indicator curve is represented by a theoretical equation containing four parameters. The four parameters of the theoretical equation are functions of the unknown quantities Q, Q₀, V₁, and V₂. When the numerical values of the four parameters of the theoretical equation are obtained from a numerical analysis of the experimental curve, one obtains a system of four equations in four unknowns. In principle, a unique solution of the physical system under investigation is possible.

On the other hand, if the concentration sampled is that of the reservoir which does not receive the injection (A-V or V-A), the theoretical equation of the experimental curve contains only three parameters. Analysis of the experimental curve will yield the numerical values of the three parameters of the curve, giving three equations in four unknowns. The solution is indeterminate.

**Sufficient and Insufficient Experiments**

We will define as a "complete solution" one which yields the values of all the parameters of the system under investigation. An "incomplete solution" yields some, but not all. An experiment which yields a complete solution is a "sufficient experiment." An "insufficient experiment" is one which cannot possibly yield anything but an incomplete solution. The product of an insufficient experiment is an "insufficient sequence" or an "insufficient curve." Thus, if the injection is atrial and the sampling is ventricular or immediately distal to the ventricle, the experiment yields an insufficient sequence. If the sampling is done through a catheter or far downstream, the experiment yields an insufficient curve.

In general, an experiment is insufficient if it yields a number of equations which is smaller than the number of unknowns. However, even if the number of equations equals the number of unknowns, it is possible to have a curious type of insufficiency, which we term "insufficiency of identification." Assume a system consisting of two reservoirs of volumes V₁, V₂ in series connected by a short section of tubing and supplied with an inlet tube and an outlet tube. Let the volume-rate of flow be Q. We will show that it is not possible to design a single elementary indicator-dilution experiment that will yield a complete solution of this system.

If an injection is made into the first reservoir and sampling is done either in the first reservoir or in the connecting short tube, the experimental concentration curve (assuming perfect mixing) will satisfy equation 56:

\[ C₁ = \left(\frac{I}{V₁}\right) e^{-Q/V₁} \tag{56} \]

Numerical analysis of the experimental curve will yield the numerical values of I/V₁ and of Q/V₁. Thus, the values of Q and of V₁ may be solved for, but the value of V₂ remains unknown.

If an injection is made into the second reservoir and sampling is done within the second reservoir or at the outlet, the experimental curve will satisfy the equation:

\[ C₂ = \left(\frac{I}{V₂}\right) e^{-Q/V₂} \tag{57} \]
Analysis of this curve will yield the values of $Q$ and of $V_2$; the value of $V_1$ remains unknown.

Finally, if the indicator is injected into the first volume and sampling is done in the second volume, the experimental curve will satisfy the equation:

$$C_2 = \frac{I}{V_1 - V_2} e^{\frac{Q}{V_1}} - \frac{I}{V_1 - V_2} e^{\frac{Q}{V_2}}. \quad (58)$$

Analysis of the experimental curve will yield the numerical values of $I/(V_1 - V_2)$, of $Q/V_1$, and of $Q/V_2$. This will provide a system of three simultaneous equations in three unknowns, and the values of $V_1, V_2, Q$ may be calculated. Nevertheless, the solution is incomplete for the following reason:

Assume that the serial order of the two reservoirs is reversed. Let the injection again be made into the proximal reservoir and the sampling be done in the distal reservoir. The equation of the experimental curve may be obtained from equation 58 by interchanging the symbols $V_1$ and $V_2$. When this is done, the resulting equation is identical with equation 58. In other words, for a given flow rate $Q$ and an indicator dose $I$, the output from the system is completely independent of the serial order of the two reservoirs. This is a case of insufficiency of identification, since the indicator-dilution experiment will disclose the magnitude of the two volumes but will not disclose whether the distal or proximal reservoir is the larger.

It should be mentioned that this peculiarity is not limited to a system consisting of two simple reservoirs in series with ideal mixing. If a system consists of any two structures in series, then, for a given input $I$ and a given flow $Q$, the output curve is completely independent of the serial order of the two structures in the series. Finally, if the system consists of more than two structures in series, the output curve is the same for all possible permutations of the structures in the system. The proof is given in Appendix 4.

**General Pulsatile Model and Indeterminacy**

We return to the question of whether the indeterminacy of some types of experiments is a peculiar characteristic of our two particular models. It is possible to produce other models of the pulsating heart. In particular, it is possible to introduce one more parameter, namely, a time parameter, specifying the sequence and rate of events within a cycle. Whatever the model, the concentrations of the indicator in the two chambers at the end of a given cycle are related linearly to the concentrations at the end of the preceding cycle, as illustrated in the following two equations:

$$a_{i+1} = S_1 a_i + T_1 v_i \quad (59)$$

$$v_{i+1} = S_2 a_i + T_2 v_i \quad (60)$$

where $S_1, S_2, T_1, T_2$ are functions of the unknown parameters of the model.

The general solution of this system of a pair of difference equations has the same structure, independent of the nature of the model, namely:

$$a_i = A_1 R^i + B_1 R'^i \quad (61)$$

$$v_i = A_2 R^i + B_2 R'^i \quad (62)$$

where $R$ and $R'$ are functions of the parameters of the difference equations and, consequently, functions of the unknown parameters of the model. On the other hand, the coefficients $A_1, B_1, A_2, B_2$ are functions of the unknown parameters of the heart, and they also contain two arbitrary constants. When the site of injection is specified, a particular solution is obtained in which the four coefficients do not contain any arbitrary constants.

In an elementary experiment, an injection is made into one of the two chambers. At zero time ($i = 0$), the concentration in the other chamber is zero. Consequently, the theoretical formula for the sequence of concentrations in the other chamber contains two coefficients which are equal in magnitude but opposite in sign. The sampled concentration, starting from zero, increases to a maximum, then decreases (fig. 4, right panel). The formula is degenerate in that it has only three numerical parameters. Since any model of a pulsatile heart must contain at least four volume parameters, sampling the concentration of the compartment which does not receive the injection is bound to yield a system of only three

*Circulation Research, Volume IX, May 1961*
equations in at least four unknowns, and the solution is indeterminate.

When the sampling and injection sites are the same (fig. 4, left panel), the curve decreases monotonically. Its theoretical equation contains the sum of two exponentials and contains four independent parameters. Analysis of the curve yields four equations in four unknown parameters of the heart, and there is a definite solution.

Indeterminacy of the Value of \( L \)

It was shown earlier that an A-V experiment yields an insufficient curve. It is possible to construct an infinite number of hearts, each of which will show the same sequence in an A-V experiment.

Inspection of equation 20 will show that any heart whose parameters will satisfy the following three equations will yield the same A-V sequence:

\[
\frac{e}{V_s \cdot \sqrt{v}} = \text{constant} = \frac{e^0}{V_s^0 \cdot (\sqrt{v})^0} \quad (63)
\]

\[R = \text{constant} = R^o \quad (64)\]

\[R' = \text{constant} = R'^o \quad (65)\]

where the quantities marked with an asterisk are the values of the respective parameters calculated from the experimental curve.

As an illustration, consider the heart, the four elementary sequences of which are shown in figure 1:

\[420; \quad (64/14; \quad 70) : \quad L = 1.6 \]

\[\frac{V_s^0 \cdot (\sqrt{v})^0}{e^0} = 3.256 \quad 858 \quad L^{-1}; \quad R^o = 0.841 \quad 098; \quad R'^o = 0.365 \quad 529.\]

Figure 5 shows some of the parameters of the complete series of hearts, each of which will yield the same A-V curve. The curves are plotted against the values of \( b \) taken as the arbitrary variable. The upper panel shows certain of the volumes of the various hearts; the lower panel shows certain dimensionless ratios of the various hearts. The circles mark six hearts (I to VI), the performances of which are shown in figure 7. The solid circles represent the heart specified above (heart II).

Since the net cardiac output per beat, \( F' \), is determined by equation 27, its value is the same for all hearts, namely, 70 cc. The other three volume parameters differ from one heart to another. Of the dimensionless ratios only \( 1 - R \) is the same for all hearts in this series.

As may be seen in figure 5, the series of hearts is confined to a limited range of values of \( b \). Hearts I and VI define these two limits. In each of these two, \( L = 0 \). Heart I is defined by the condition that \( R = 1 - g = R^* = 0.841 \quad 098. \) Heart VI, at the other extreme of the series, is determined by the conditions: \( L = 0; \quad b = R^* = 0.841 \quad 098. \)

The values of \( R \) and of \( 1 - R \) are constant for the entire series. Since the ultimate downstroke slope of the curve equals \( \log R \), the slope in heart I (a nonregurgitant heart) equals \( \log (1 - g) \); the atrium is larger than the ventricle and controls the downstroke slope. In heart VI, the slope is \( \log b \) since the ventricle of this nonregurgitant heart is larger than the atrium and the ventricle controls the
HEARTS WITH COMMON A-V SEQUENCE

Figure 5

Series of hearts yielding the same A-V sequence. The (circles) indicate six hearts (I to VI), the output sequences of which are shown in the left panel of figure 7. (Double circles): heart II, which is also a member of the series shown in figure 6. All parameters are plotted against values of b. The two extreme hearts are nonregurgitant (L = 0). In this series, the value of L varies from 0 to a little over 0.38.

slope. In all other hearts, the numerical value of the downstroke slope is smaller than either Log (1 - g) or Log b and is a complex function of the dimensionless parameters of the heart.

Inspection of curve L in the lower panel of figure 5 will show that the extent of regurgitation is one of the indeterminate quantities in an A-V experiment. Furthermore, assuming that the A-V curve was obtained from heart II, it would be difficult to choose from the figure some narrow range of hearts, using physiological arguments, thereby narrowing down the range of reasonable values of L. According to this figure, the value of L may be anywhere within the range of 0 to a little over 38 per cent of the total ventricular stroke.

As was shown earlier, a V-A experiment will also give an insufficient curve. Inspection of equation 21 will disclose that it is possible to construct an infinite number of hearts, each of which must satisfy the following three conditions:

\[
\frac{\nu \cdot L}{V_r \sqrt{\nu}} = \text{constant} = \frac{\nu^* \cdot L^*}{V_r^* \sqrt{\nu^*}} \tag{66}
\]

\[R = \text{constant} = R^* \tag{67}\]

\[R' = \text{constant} = R'^* \tag{68}\]

where the quantities marked with an asterisk are those obtained from the analysis of the experimental curve.

Figure 6 shows a series of hearts, each of which will yield the same V-A sequence as that yielded by heart II of figure 5. Again, volumes are shown in the upper panel, dimensionless ratios in the lower panel. The circles mark hearts II and VII. Heart II is the same as that shown in figure 5.

The curves in the lower panel are identical to the curves in the lower panel of figure 5. This applies as well to curve K, which was not included in figure 5. The curves are identical for the following reasons: It was shown earlier (equations 19 to 22) that for a given heart, the values of R and R' are independent of the sites of injection and sampling. The two series of hearts have one heart in common (heart II). It follows that both series of heart in figures 5 and 6 must yield the same values of R and of R'. This imposes the same two conditions on the three variable, dimensionless parameters (b, g, and L) in both series. In each series there is left one degree of freedom. However, once a value of b is chosen, the corresponding heart in each of the two series must show the same values of g and L. Since K is a function of b, g, and L only, a chosen value of b fixes the value of K in both series.

Circulation Research, Volume IX, May 1961
Some of the hearts shown in figure 6 are absurd from the physiological point of view since the calculated volumes are entirely too small. This situation arises from the fact that the diagram shows the complete mathematical solution of the condition that all the hearts in the series must produce the same V-A sequence. However, the series includes a wide range of physiologically plausible hearts.

As may be seen in figure 6, the quantity \( L \) is indeterminate from a single curve. Furthermore, in a V-A experiment the net cardiac output is also indeterminate, whereas in an A-V experiment the value of \( P \) may be calculated from the experimental curve.

It should be pointed out that the issue discussed here is not whether regurgitation can be detected by a V-A experiment. Clearly, atrial sampling with ventricular injection will detect the presence of regurgitation if more than minute amounts of the indicator appear in the atrium. However, the present analysis shows that neither the extent of regurgitation nor the net cardiac output can be quantified from a V-A curve.

The indicator outputs of hearts I to VII, shown in figures 5 and 6, are presented in figure 7. The left panel shows the outputs of hearts I to VI of figure 5 (atrial injection). The A-V output of each heart in this series is the same and is represented by solid circles. The A-A output of each heart differs from that of any other in the series and is represented by curves I to VI with open circles.

Curves I and VI, which are the A-A outputs of the two extreme, nonregurgitant hearts, are pure exponentials and are represented on a semilog plot by straight lines. The other curves fall between these two. With the exception of the extreme curve VI, all A-A curves in this series approach a linear phase, in which the slope is the same as that of the linear phase of the common A-V sequence. The rate of approach to the linear phase decreases from curve I down; as a result the vertical distance from the linear part of the common A-V curve to the linear part of the respective A-A curve increases. In other words, the value of \( K \) increases progressively from heart I toward heart VI. \( K \) is infinite for heart VI, as was mentioned earlier.

The right panel of figure 7 shows the outputs with a ventricular injection of hearts II and VII of figure 6. Again, it is seen that markedly different hearts may produce the same V-A output. On the other hand, the V-V outputs differ from one heart to another.

Indeterminacy in Peripheral Sampling Experiments

When sampling is peripheral, i.e., just outside the ventricle, and injection is atrial, the terms of the sequence of concentrations \( P_i \) are identical with the corresponding terms of the \( v_i \) sequence. Since the latter sequence yields an indeterminate solution, an A-P ex-
The experiment is also insufficient; it is incapable of yielding a definite value of \( L \).

With peripheral sampling and ventricular injection, all the terms of the \( P_i \) sequence are identical with the corresponding terms of the \( V_i \) sequence except the zero term since \( P_o = 0 \) and \( V_o = \frac{1}{V_{v,r}} \). However, a complete solution of the heart may be obtained, and the experiment may be classified sufficient.

**Discussion**

We initiated the present investigation in the hope of finding a theoretical basis for the quantification of mitral regurgitation through the analysis of the properties of a single experimental indicator-dilution curve. Our analysis shows that the ultimate downstroke slope cannot be used even as an index of regurgitation, let alone for the purpose of quantifying it.

This analysis also shows that certain kinds of experiments yield curves which can give only indeterminate solutions. Unfortunately, a large majority of clinical techniques currently in use are of this type, namely, injection in the atrium or into a vein and sampling distally to the ventricle in one of the arteries.12-16, 25, 26 For this reason, we find it desirable to present a critical discussion of the chain of arguments leading to the above conclusions, omitting any unnecessary mathematical details.

It may be accepted as axiomatic that concentration curves obtained far downstream are more complicated than those obtained by sampling in the atrium, in the ventricle, or peripherally just outside the ventricle. Secondly, it is difficult to see how it is possible to analyze quantitatively a curve obtained from a real heart unless one can predict the nature of the curves obtained from idealized model hearts, i.e., hearts characterized by instantaneous and ideal mixing in each of the two chambers and by a simple periodicity of the heart cycle.

In choosing the simplest model to simulate the action of an ideal heart, we assumed that it takes at least four anatomical parameters to define the behavior of a regurgitant heart: the maximum volume of the atrium, the residual volume of the ventricle, the net forward output per beat, and the volume of backward flow per beat. The generalized heart model represents a nonregurgitating heart when the fourth parameter is equated to zero. In the simplest model (our model I), the delivery of blood from the vein to the atrium and from the atrium to the ventricle constitutes two consecutive events. In our model II, the two flows are concurrent. We have examined the behavior of model II sufficiently to establish the fact that the sequences yielded by this model are qualitatively the same as those yielded by model I. The differences are only quantitative and become small when the heart is large, compared with the net forward output per beat. For this reason, we spent most of our efforts on the analysis of curves obtained from model I.

It is desirable to call attention to the fact that the sequences to be expected from a given experiment performed with a specified mathematical model are completely defined by the model itself. The subsequent mathematical treatment is straightforward and does not require additional assumptions or approximations.

Once the model is defined, it is possible to
calculate the ultimate downstroke slope for any heart or for any series of hearts in which one or more parameters are varied in a systematic fashion. Analysis shows that the calculated slope exhibits the following features:

1. If the only variable in a series of hearts is the volume of retrograde flow, then the ultimate slope is insensitive to the degree of regurgitation.

2. If the net output per beat and the "needle-to-needle volume" are kept constant and, consequently, there still remain two degrees of freedom in choosing the heart, then, for any given downstroke slope, it is possible to produce at will another heart with more, less, or no regurgitation. It becomes obvious that quantification or regurgitation must depend not merely on an examination of the downstroke slope but also on a careful examination of the curve as a whole.

In order to solve for the parameters of the heart from the experimentally obtained sequence of concentrations, it is necessary to match the experimental sequence against the appropriate theoretical equation. The theoretical equation is obtained by solving the pair of first order homogenous difference equations characteristic of the adopted model. The general solution for all elementary experiments with a single instantaneous injection must have the structure: \( C_i = (\text{constant}) \cdot R_i + (\text{constant})_2 \cdot R^n \). Thus, no matter what the detailed nature of the two-chamber pulsatile model, the equation for any experimental sequence contains at most four parameters. If the sampled concentration has zero value at zero time, two of the parameters must be equal in magnitude but opposite in sign. It follows that an experiment of this type is bound to yield insufficient information to solve for the four unknown parameters. A-V, V-A, and A-P experiments yield insufficient information. On the other hand, the following experiments yield sufficient information in an ideal experiment: A-A, V-V, V-P.

It should be emphasized that insufficiency of information does not imply complete absence of information. With a system of three equations in four unknowns, there is only one degree of freedom left, and some information about the unknowns is available. Thus, correct values of \( F \), the net output per stroke, may be calculated from A-V and A-P sequences, even though the two sequences are insufficient for a complete solution of the heart. The question naturally arises whether the fraction regurgitated per stroke, i.e., the quantity \( L \), may not be another unknown whose value can be calculated even from an insufficient experiment. Rather than use a mathematical argument to prove that this is not so, it will suffice to call attention to the fact that given an insufficient sequence, it is possible to construct an infinite series of hearts with varying values of \( L \), each of which will yield the same sequence of concentration (see figures 5 and 6).

Whereas it takes four parameters to define a regurgitant heart, it takes only three parameters to define a nonregurgitant heart. Thus, it takes three parameters to determine the ultimate downstroke slope of a curve obtained from a nonregurgitant heart. Korner and Shillingford, using the standard multiple regression technique and data from human indicator-dilution curves in the absence of regurgitation, derived an equation which predicts the downstroke slope in terms of two parameters only: the net cardiac output per minute and the needle-to-needle volume. The interesting question arises as to why it is possible to obtain a fair correlation between actual slopes and slopes predicted from a two-parameter equation.

We offer the following explanation: Assume a population of nonregurgitant hearts, each of which can be specified in terms of three parameters. Assume, next, that in this population all the hearts satisfy precisely some condition. For the sake of concreteness, assume that the entire population shows precisely the same ratio of residual to maximum ventricular volumes. In that case, the number of independent parameters is only two. With two parameters specified, it should be possible to predict precisely the value of the downstroke slope in terms of two parameters only. Assume, next, that the restriction is somewhat relaxed: Let the ratio of the two volumes be...
not precisely the same in all hearts, but let it be distributed about some mean value. In that case a two-parameter equation will not yield precise values of the downstroke slope. However, the equation will still yield statistically satisfactory values of the slope in the sense that there will be rather high correlation between observed slopes and those predicted by the equation. Thus, the existence of equations which are statistically satisfactory in correlating the downstroke slope with only two parameters does not contradict the conclusion that it takes three parameters to define the slope accurately.

In view of the use of mechanical hearts for the purpose of finding a method for evaluating regurgitation from a single indicator-dilution curve, it should be pointed out that, at best, a mechanical heart is only a mechanical analog of a mathematical heart. It follows that given a dilution curve obtained from an A-V experiment with an unknown mechanical heart, it is not possible to evaluate the extent of regurgitation. The question arises as to the explanation of the fact that investigators using a mechanical pump can obtain an equation which satisfactorily relates the shape of the experimental curve with only two parameters of the mechanical heart. It is doubtful, however, that the same equation will be valid for the analysis of a single A-V curve turned out by some other model whose adjustments are of a different nature. Thus, there is no irreconcilable conflict between the mathematical principle that, in general, it is not possible to quantify regurgitation from a single A-V curve and the fact that the performance of some particular model can be quantified with the use of an equation obtained from a sufficiently large number of curves produced by the particular model under investigation. These theoretical conclusions are supported, in part, by the experimental observations made by Hoffman and Rowe while working in Shillingford's laboratory. These workers demonstrated that estimates of backflow by the Korner-Shillingford method of calculation, with forward flow and needle-to-needle volume kept constant, were altered by changing from one mechanical model to another, e.g., when the type of proximal chamber was changed from a rigid to an elastic one. Shillingford has also recently recognized that estimations of valvular incompetence in individual patients by the Korner-Shillingford technique may be subject to a large error.

Summary

A theoretical analysis of indicator-dilution curves produced by a pulsatile, two-chamber mathematical model simulating a normal in vivo heart and one with atrioventricular valve regurgitation is presented. A set of difference equations is developed expressing the concentrations within the chambers at the end of each cycle in terms of the number of cycles or beats. It is shown theoretically that the downstroke slope of the dilution curve is insensitive to the extent of regurgitation. Solution of the difference equations for the parameters of the heart governing the curve (chamber volumes, forward output, and regurgitant flow), when the dilution curve is sampled from the chamber in which the injection is made, is achieved through a system of four equations in four unknowns. Sampling of the concentration curve from the chamber which does not receive the injection produces a theoretical curve giving three equations in four unknowns and results in an indeterminate solution. As a consequence, quantification of atrioventricular valve regurgitation through analysis of a single distal
indicator-dilution curve following proximal injection cannot be accomplished.

Appendices

Appendix 1. Derivation of Two Difference Equations

At the end of the i-th cycle, the volume of the ventricle is \( V_v \), the concentration of the indicator in the ventricle is \( v_i \), and the amount of indicator in the ventricle is \( bV_vv_i \). During the next cycle, the atrium delivers the volume \( cV_v \) containing the concentration \( a \), and a total amount of indicator \( bV_v \). When delivery of blood from the atrium is complete, the ventricle is at its maximum volume \( V_v \), and contains \( (bV_vv_i + cV_va) \) units of indicator. Thus, just before contraction, the concentration of the indicator is:

\[
\frac{bV_vv_i + cV_va}{V_v} = a_i + bv_i . \quad (A-1.01)
\]

During the contraction of the ventricle, there is expulsion of blood into the atrium and into the vein, but the concentration does not change. Hence, the equation for \( v_{i+1} \) is:

\[
v_{i+1} = cai + (A-1.02)
\]

At the end of the i-th cycle, the volume of the atrium is \( V_a \), the concentration of the indicator is \( a_i \), and the amount present is \( V_a \). During the next cycle, the following events take place: The atrium delivers to the ventricle a volume of blood \( gV_a \), thus losing \( gV_a \) units of indicator. When the ventricle contracts, it returns to the atrium a volume \( gLV_v \) of blood, carrying the concentration \( V_{j+1} \), the amount of indicator returned by the ventricle is \( gLV_vv_{i+1} \). When the cycle is complete, the volume of the atrium is \( V_a \) again, and the amount of indicator present is \( V_a a_{i+1} = gV_va_i + gLV_vv_{i+1} \). Division of the amount present by the volume yields the formula:

\[
a_{i+1} = (1 - g)a_i + gLV_{v_{i+1}} . \quad (A-1.03)
\]

Substitution of equation A-1.02 for \( v_{i+1} \), in equation A-1.03 yields the formula:

\[
a_{i+1} = (1 - g + gLe)a_i + gLbKi . \quad (A-1.04)
\]

The derivation of the difference equations for model II is presented elsewhere.29

Appendix 2. Derivation of the Formulas for \( K \) and for \( R \)

By hypothesis, when the cycle number \( i \) is large enough, the ratio \( v_{i+1}/v_i \) equals some value \( K \) to within any desired degree of accuracy. Assuming that the value of \( i \) is large enough, the concentrations in the atrium and in the ventricle are \( a_i \) and \( K a_i \), respectively. Application of the two difference equations (A-1.02 and A-1.04) will yield the formulas of the concentrations at the end of the next cycle:

<table>
<thead>
<tr>
<th>End of cycle no.</th>
<th>Concentration in atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>( i )</td>
<td>( a_i = a_1 )</td>
</tr>
<tr>
<td>( i+1 )</td>
<td>( a_{i+1} = (1 - g + gLe)a_i + gLbKi )</td>
</tr>
</tbody>
</table>

Concentration in ventricle:

\[
v_i = K a_i \]

\[
v_{i+1} = cai + bKa_i . \quad (A-1.01)
\]

For large values of \( i \), the ratios become stable; it follows that, at the end of cycle \( i+1 \), \( a_{i+1} \) and \( v_{i+1} \) must meet the condition that \( v_{i+1} = K a_{i+1} \). Substitution of the two concentrations at the end of cycle \( i+1 \) yields the following quadratic equation in \( K \):

\[
e + bK = K(l - g + gLe + gLbK) . \quad (A-2.01)
\]

The quantity \( l - g + gLe \) appears very frequently and is represented by the single symbol \( r \). Substitution of \( r \) and rearrangement of terms yields:

\[
gLbK^2 + (r-b)K - c = 0 . \quad (A-2.02)
\]

This quadratic equation has two roots:

\[
K = \frac{-(r-b) \pm \sqrt{(r-b)^2 + 4gLbc}}{2gLb} . \quad (A-2.03)
\]

One of the two roots is positive, the other is negative. The negative root is discarded, and the positive root is the desired solution for \( K \):

\[
K = \frac{-(r-b) + \sqrt{(r-b)^2 + 4gLbc}}{2gLb} . \quad (A-2.04)
\]

The formula for \( R \) may be obtained directly from the preceding two-cycle table. By definition, \( R \) is the ultimate ratio of two successive concentrations, when \( i \) is very large. Since the table was constructed on the hypothesis that \( i \) is large enough, \( R = a_{i+1}/a_i \):

\[
R = \frac{a_{i+1}}{a_i} = (1 - g + gLe) + gLbK . \quad (A-2.05)
\]

Substitution of equation A-2.04 for \( K \) yields equation A-2.06:

\[
R = \frac{(r+b) + \sqrt{(r-b)^2 + 4gLbc}}{2gLb} . \quad (A-2.06)
\]

To prove that the ultimate ratio of two successive concentrations is the same in the ventricle as in the atrium, consider the ratio \( v_{i+1}/v_i \) in the same two-cycle table:

\[
\frac{v_{i+1}}{v_i} = \frac{~ - bK}{K} = \frac{c}{K} + b
\]
From equation A-2.07, one obtains a simple formula for the relation between $R$ and $K$: $$\frac{e + bK}{K} = R. \quad (A-2.08)$$

Solution of this equation for $K$ in terms of $R$ yields equation A-2.09:

$$K = \frac{e}{R-b}. \quad (A-2.09)$$

$R$ is the ultimate ratio of two successive concentrations. Since the concentrations eventually keep diminishing, the value of $R$ is less than unity. For this reason, the following inequality holds:

$$K = \frac{e}{R-b} > \frac{e}{1-b} = \frac{e}{c} = 1. \quad (A-2.10)$$

The quantity $K$, which represents the ultimate value of the ratio $v_a/v_a$, is larger than unity, independently of the magnitudes of the heart parameters. Thus, in any experiment, when continued long enough the ventricular concentration eventually becomes larger than the atrial concentration, and finally, the ratio of the two concentrations approaches the constant value $K$.

**Appendix 3. Formulas for Nonregurgitant Hearts**

Formulas for nonregurgitant hearts may be obtained directly from equations 13 to 22 by substitution of the value: $L = 0$. It is important to keep in mind the definition of the symbol $\sqrt[+]{ }$, given in equation 14. This symbol is defined as the positive root of the expression under the square root. When $L$ is a finite quantity, there is no ambiguity. For this reason, the following inequality holds:

$$K = \frac{e}{R-b} > \frac{e}{1-b} = \frac{e}{c} = 1. \quad (A-2.10)$$

The quantity $K$, which represents the ultimate value of the ratio $v_a/v_a$, is larger than unity, independently of the magnitudes of the heart parameters. Thus, in any experiment, when continued long enough the ventricular concentration eventually becomes larger than the atrial concentration, and finally, the ratio of the two concentrations approaches the constant value $K$.

**Appendix 4. Independence of the Output of a System from the Serial Arrangement of Structures Within the System**

Assume that a flow system consists of a series of structures $K$, $L$, $M$, $N$, in the indicated order. There is a constant flow through the system, at some volume rate $Q$. As indicator is injected proximally to the system at some rate $I(t)$, not necessarily constant, the indicator-output concentration at a distal point will be some function of time, $C(t)$. The four structures can be arranged in some other serial order, and there are 24 different permutations of the four structures. It can be shown that, for the same input $I(t)$ and rate of flow $Q$, the output, $C(t)$ is independent of the serial arrangement of the structures.

Consider a system consisting of a single structure only, say $K$. Assume that a proximal instantaneous injection of infinitesimally small quantity $dI$ is made at zero time. The concentration-output of the structure will be some time function $C(t)$ which may be represented by equation A-4.01:

$$C(t) = dI . D_k(t) \quad (A-4.01)$$

The function $D_k$ is a characteristic of the structure $K$. It is to be understood that it is also a function of the rate of flow $Q$.

If the injection is made not at zero time, but at some time $T$, the output-concentration is the same function of $(t-T)$:

$$C(t) = dI . D_k(t-T) \quad (A-4.02)$$

The other structures have similar characteristic functions $D_L$, $D_M$, $D_N$. These functions need not be simple analytical functions. For instance, if $K$ happens to be a long tube, $D_k$ has the following properties: The function is equal to zero up to the time when the crest of the indicator cone reaches the sampling site. At that time, the value of the function increases rapidly, then proceeds to decrease monotonically to a value zero at infinite time.

Consider, next, a system consisting of structures $K$ and $L$, arranged in series:

$$1 \quad K \quad 2 \quad L \quad 3 .$$

Equation 41 may be obtained directly from equation 40 by imposing the condition that the atrium is the same size as the ventricle. This leads to the relations: $c = g$ and $1-g = b$. When these values are substituted in equation 40, an indeterminate ratio $O/O$ appears in the equation. Evaluation of this indeterminate ratio converts equation 40 into equation 41.
The symbols 1, 2, and 3 represent, respectively, the proximal injection site, a short connecting tube, and the distal sampling site. Assume that an infinitesimal injection $dl$ is made at 1 during an infinitesimally short time $dt$. There is no loss in the generality of the proof if it is assumed that the injection is carried out at zero time. Let the output of K at some time $t_2$ be $C_2(t_2)$. This function also represents the input-concentration reaching structure L at the time $t_2$.

During the interval between $t_2$ and $t_2 + dt_2$, the amount-input into structure L is $dl_2 = Qdt_2 \cdot C_2(t_2)$. Substitution of equation A-4.01 for $C_2$ yields equation A-4.03:

$$dl_2 = Qdt_2 \cdot [dI'D K(t_2)] , \quad (A-4.03)$$

where $dl_2$ is an infinitesimal of second order.

The concentration-output of structure L is some function $C_3(t_3)$ of the time of sampling, $t_3$, at site 3. The contribution to the value of $C_3(t_3)$ which is due to the input into structure L during the interval $dt_2$ may be obtained by combining equation A-4.03 with an equation similar to equation A-4.02:

$$dC_3(t_3) = dI_2'D L(t_3 - t_2) = [Qdt_2'dI-D K(t_2)] \cdot DL(t_3 - t_2) . \quad (A-4.04)$$

The function $C_3(t_3)$ may be evaluated by adding up the contributions made to $C_3$ during all the intervals $dt_2$, from $t_2 = 0$ to $t_2 = t_3$, in other words, by integrating equation A-4.04 with respect to $t_2$; in this integration the only variable is $t_2$; $t_3$ is constant.

$$C_{3KL}(t_3) = Q'dl' / D_r(t_2) \cdot D K(t_3 - t_3) . \quad (A-4.05)$$

where $C_{3KL}(t_3)$ is the concentration-output at site 3, at time $t_3$, with the two structures arranged in the order L, K.

Assume another flow system, in which the order of the two structures is reversed:

$$C_{3LK}(t_3) = Q'dl' / D_L(t_3) \cdot D K(t_3 - t_3) . \quad (A-4.06)$$

To prove that the right sides of equations A-4.05 and A-4.06 are identically equal, we introduce a change of variables. Let $t_3 - t_2 = x$; $t_2 = t_3 - x$; $dt_2 = -dx$;

Lower limit: replace $t_2 = 2$ with $x = t_3$;

Upper limit: replace $t_2 = 0$ with $x = 0$.

Comparison of the formulas for $C_{3KL}(t_3)$ (equation A-4.05) and for $C_{3KL}(t_3)$ (equation A-4.06) will show that the right sides are identical in structure, with the only difference that the dummy letter, $t_2$, in the former is replaced by the dummy letter $x$. These disappear upon integration and substitution of limits. For this reason the two functions are identically equal for all values of $t_3$. For a given infinitesimal injection $dl$ and a given value of $Q$, the output of the system K, L is the same as the output of the system L, K for all values of $t_3$.

Since a continuous injection $I(t)$ is mathematically equivalent to an infinite series of infinitesimal injections $dl$, and since it was proved that the contribution of each infinitesimal injection to the output function of the two-structure system is independent of the order of the two structures, the indicator-output of a two-structure system is independent of their order, even if the input into the proximal system is some continuous function $I(t)$.

Consider, next a flow system consisting of four structures, K, L, M, N, arranged in the indicated order. An interchange of any two adjacent structures, say L and M, will certainly not change the input into the system consisting of these two structures. By the arguments given previously, the output of the two-structure system will also remain unaffected. It follows that the output of the four-structure system will not be affected by an interchange of any two adjacent structures. Since any permutation of the structures can be obtained from the original permutation by a series of interchanges of two adjacent structures, it follows that all 24 permutations will show the same output for a specified input $I(t)$ and a specified constant flow $Q$.

Appendix 5. Indeterminacy of Identification in a Two-Reservoir System, with Back Flow

In the two-reservoir system, with back flow $Q_b$, the input and net output rates are $Q$. The rate of forward flow from the first to the second reservoir is $Q + Q_b$. After the injection is com-
pleted, and independently of the site of injection or magnitude of the dose, the concentrations in the first and in the second reservoir obey the following two differential equations:

\[
\frac{dC_1}{dt} = -\frac{Q + Q_0}{V_1} C_1 + \frac{Q_0}{V_1} C_2 \quad (A-5.01)
\]

\[
\frac{dC_2}{dt} = \frac{Q + Q_0}{V_2} C_1 - \frac{Q + Q_0}{V_2} C_2. \quad (A-5.02)
\]

The two equations may be classified as a system of two simultaneous homogeneous differential equations with constant coefficients. The four constant coefficients contain, amongst them, the four unknown parameters of the system. The explicit solution of this system is laborious and cumbersome and is not needed for the argument which follows.

The solution has the following structure:

\[
C_1 = A_1 e^{k_1 t} + B_1 e^{k_2 t} \quad (A-5.03)
\]

\[
C_2 = A_2 e^{k_1 t} + B_2 e^{k_2 t} \quad (A-5.04)
\]

where the quantities \( k_1 \) and \( k_2 \), appearing in both equations, are the two roots of the characteristic quadratic equation of the system A-5.01, 5.02. They are functions of the parameters of the original differential equations and, therefore, functions of the unknown parameters of the system; the functions \( k_1 \) and \( k_2 \) are independent of the site of injection or of the magnitude of the dose. On the other hand, the coefficients \( A_1, B_1, A_2, B_2 \) are functions of the parameters of the system and of the magnitude of the dose. Furthermore, their structures and values depend upon the site of injection.

The two equations may be represented by a single equation:

\[
C_i = A_i e^{k_i t} + B_i e^{k_2 t} \quad (i = 1 \text{ or } 2). \quad (A-5.05)
\]

If \( C_i \) is the concentration of the reservoir which does not receive the injection, then \( B_i = A_i \), since the equation must satisfy the condition that the concentration is zero at zero time. Thus, the equation contains three independent parameters, \( A_1, k_1, k_2 \). Analysis of the experimental curve will yield the numerical values of these three quantities, thus providing three equations in four unknowns. The solution is indeterminate.

On the other hand, if \( C_i \) is the concentration of the reservoir which receives the injection, the equation contains four independent parameters, and analysis of the experimental curve will yield four equations in four unknowns. A definite solution of the system of unknowns can be obtained.

References


MITRAL REGURGITATION

Some Theoretical Aspects of Quantification of Mitral Valve Regurgitation by the Indicator-Dilution Method: Sufficient and Insufficient Experiments
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Circ Res. 1961;9:639-663
doi: 10.1161/01.RES.9.3.639

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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