Measurement of Mitral Regurgitation by Indicator-Dilution Techniques

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CONSIDERABLE progress has been made in recent years in the quantitative estimation of certain cardiovalvular abnormalities by cardiac catheterization. The quantitative determination of mitral regurgitation has not yet reached a similar status despite a substantial amount of experimental effort. This article will give theoretical bases for determination of mitral regurgitation by indicator-dilution techniques as well as experimental demonstrations of the effects of violating these bases.

A variety of proposals have been made for determining the amount of regurgitant flow. These have involved single or continuous injections of indicator in the left atrium or left ventricle with recordings of indicator concentrations in one or both chambers of the left heart or in peripheral arteries. Attempts have been made to correlate the shape of the concentration curve or the areas enclosed by the concentration curves with the severity of mitral regurgitation. The following analysis of an idealized two-chamber pumping system provides a theoretical background for evaluation of these methods.

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Supported in part by the U.S. Army Signal Corps, the Air Force Office of Scientific Research, and the Office of Naval Research (Research Laboratory of Electronics); U.S. Army, Navy, and Air Force under Air Force Contract AF19 (604)-5200 (Lincoln Laboratory); Life Insurance Medical Research Fund, American Heart Association, and National Heart Institute (Grant H-450) (Harvard Medical School and Peter Bent Brigham Hospital).

Received for publication May 11, 1961.

Mathematical Models of Cardiac Flow and Their Limitations

A complete solution of fluid flow through the heart would require formulating differential equations of fluid dynamics and subjecting these to the constraints imposed by the cardiac walls in motion and the motion of the valve leaflets. This would require a much more extensive knowledge of the physical parameters of the heart than currently exists; e.g., the details of physical movement of the heart walls at each instant of the cardiac cycle would have to be known.

A less complete but hopefully adequate model of cardiac flow is concerned only with the total volume of fluid transported between chambers or out of each chamber during each intersystolic period or with the time-averaged rate of flow.

To make the model mathematically workable, five simplifying assumptions concerning the nature of the flow are necessary. These assumptions are listed and discussed in the following paragraphs:

Complete Mixing

Assumption. The indicator contained within a chamber at any instant of time is uniformly distributed within that chamber.

Discussion. This assures that the measured movement of indicator represents the measured movement of blood. If the indicator is not uniformly dispersed within the chamber, indicator concentration measurements will be a function of sample location and may be meaningless. Although placement of the sampling instrument near the point of entry of fluid into the chamber (i.e., the valve) might appear to yield a valid measurement independent of mixing conditions in the chamber, Appendix E shows that this is generally untrue. The assumption of good mixing is implicitly necessary in the quantitative employ-
ment of all indicator-dilution techniques known to the authors, although it is rarely stated. To the extent that mixing is incomplete, the proposed methods all fall short of quantitative reality.

Repetitive Cardiac Action

Assumption. At one or more points in the cardiac cycle one can define chamber volumes (e.g., end-diastolic volumes) and systolic flows which repeat each beat.

Discussion. The assumption that the heart motions are nominally repetitive from beat to beat is generally true. Although the pumped volume may vary from one beat to the next, the minute flow remains relatively constant under steady-state conditions. Exercise or excitement can affect the heart rate and the volume pumped per beat. If arrhythmias are present, the effect of beat-to-beat irregularities can be minimized by averaging the results of a number of measurements taken in rapid succession. The importance of any stroke-by-stroke variations should therefore weight the evaluation of particular methods for quantifying mitral regurgitation.

No Recirculation

Assumption. The circulatory system is considered to be open-ended, and the effects of indicator recirculation can be ignored.

Discussion. There is always recirculation of indicator in the physiological system. However, the concentration curve often attains its asymptotic shape \((Ke^\alpha)\), where \(K\) is a constant) before recirculation can affect the measurements. The curve can then be extrapolated to zero and the recirculation discounted. See Stephenson\(^8\) for other techniques of dealing with recirculation.

Conservation of Indicator

Assumption. All the indicator entering the left heart remains in the bloodstream and is eventually flushed into the aorta; none of it escapes through, or is stored in, the heart walls.

Discussion. Calculations of flow by indicator-dilution techniques will be in error if some of the indicator escapes through the heart wall while being transported from injection site to sample site. There is ample evidence that indicators which are bound to proteins, such as dyes or isotopes, do remain in the bloodstream. Goodyer et al.\(^9\) have found negligible loss of heat indicator through the heart walls. However, they noticed what seemed to be a reversible exchange of heat between the blood and cardiac tissue during thermo-dilution measurements; i.e., heat is given up to the heart wall and returned to the bloodstream. Such an effect will distort the shape of the curve. Flow and other measurements dependent on the area under the concentration curve will be unaffected, provided that the "stored" indicator is released before recirculation occurs. Other shape-dependent methods must be more carefully assessed.

No Abnormal Sources or Sinks of Fluid

Assumption. There are no disorders (other than mitral regurgitation) that would provide additional sources or sinks of fluid in the left heart.

Discussion. Aortic regurgitation, for instance, provides another source of blood to the left ventricle. Consideration of this would require an appropriate modification of the mathematical model. Cardiac shunts would also require modification of the analysis. Neither tricuspid regurgitation nor mitral stenosis invalidates the following analysis, since neither of these defects adds any flow pathways to the left heart. No assumptions are made that constrain variations in chamber volume, other than that the variations are repetitive.

Continuous-Flow Model

In the model analyzed in this section, fluid flows continuously (see fig. 1) rather than intermittently. As assumed, the chamber volumes are invariant with time; these volumes correspond to end-diastolic volumes in the physiological system. This gross approximation to the cardiac flow is motivated by the resulting mathematical simplification; the behavior of the indicator concentration curves can be discussed much more easily here than in the intermittent-flow model. An intermit-
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Figure 1

Two-chamber flow system.

Figure 2

Analog indicator curve simulator. The voltages $\alpha(t)$ and $\beta(t)$ correspond to atrial and ventricular indicator concentrations. Resistances $R_1$, $R_2$, and $R_3$ correspond to $1/F_{BA}$, $1/F_F$, and $1/F_T$. Capacitances $C_A$ and $C_B$ correspond to $V_A$ and $V_B$.

tent flow model will be discussed later in this paper.

$F_F$ is the net forward flow (cardiac output) in units of volume per time. Since there are no changes in chamber volumes, the flow entering the system must be the same as that leaving the system. $F_{BA}$ is the flow regurgitated from chamber B (ventricle) to chamber A (atrium). $F_T$, the sum of the regurgitant and forward flows, is the total flow from the atrium to the ventricle. For ease of visualization, consider $F_T$ to be flowing through one short length of pipe connecting the two chambers while $F_{BA}$ flows simultaneously through another. The assumptions mentioned in the preceding section apply to this model.

Let $\alpha(t)$ be the instantaneous concentration of indicator in the atrium.

Let $\beta(t)$ be the instantaneous concentration of indicator in the ventricle.

Let $V_A$ be the volume of the atrium, analogous to the volume at the end of atrial diastole.

Let $V_B$ be the volume of the ventricle, analogous to the volume at the end of ventricular diastole.

The rate of increase of indicator in the atrium (volume $\times$ rate of change of indicator concentration) is equal to the difference between the rate at which indicator enters the chamber (regurgitant flow $\times$ ventricular concentration) and the rate at which it leaves (total flow $\times$ atrial concentration).

$$V_A \frac{d}{dt} \alpha(t) = F_{BA} \beta(t) - F_T \alpha(t). \quad (1A)$$

Similarly, for the ventricle,

$$V_B \frac{d}{dt} \beta(t) = F_T \alpha(t) - F_T \beta(t). \quad (1B)$$

The solution of these equations (Appendix B) for ventricular concentration is for an initial injectate quantity $Q$ at $t = 0$ in the atrium,

$$\beta(t) = \frac{F_T Q}{2V_A V_B \delta} [e^{s_1 t} - e^{s_2 t}], \quad (2A)$$

where

- $s_1 = -\sigma + \delta$
- $s_2 = -\sigma - \delta$
- $\sigma = \frac{F_T (V_A + V_B)}{2V_A V_B}$
- $\delta = \frac{\sqrt{F_T [F_T (V_A - V_B)^2 + 4F_{BA} (V_A + V_B)^2]} + F_{BA} (V_A + V_B)^2}{2V_A V_B}$.

Similarly, for an initial quantity $Q$ of indicator placed in the ventricle at $t = 0$,

$$\beta'(t) = \frac{Q}{2V_B \delta} \left\{ \left[ \frac{F_T (V_B - V_A)}{2V_A V_B} + \delta \right] e^{s_1 t} + \left[ \frac{F_T (V_A - V_B)}{2V_A V_B} + \delta \right] e^{s_2 t} \right\}. \quad (2B)$$

For all positive values of flows and volumes, $s_1$ and $s_2$ are negative numbers; hence, $e^{s_1 t}$ and $e^{s_2 t}$ are both decaying exponentials. From physical considerations this is obvious; the indicator concentration must eventually fall to zero in a nonrecirculatory system. Since $s_1$ is always smaller in magnitude than $s_2$, the $e^{s_1 t}$ term is dominant as $t \to \infty$.

The asymptotic derivative of the logarithm of $\beta(t)$ is

$$\lim_{t \to \infty} \frac{d}{dt} [\ln \beta(t)] = s_1$$

(''ln'' denotes natural log., i.e., log. to the base $e$).

The areas enclosed by the concentration curves are useful parameters (Appendix C).
Following either atrial or ventricular injection:

\[ B = \int_0^\infty \beta(t) \, dt = \int_0^\infty \beta'(t) \, dt = Q/F_P. \]  

(3A)

The area enclosed by \( \alpha(t) \) following atrial injection is also \( Q/F_P \). Following injection into the ventricle, however, the area under the atrial concentration curve is

\[ A = \int_0^\infty \alpha(t) \, dt = \frac{F_{BA}}{F_T} \frac{Q}{F_P} = \frac{F_{BA}}{F_T} B. \]  

(3B)

It can be shown that equations 3A and 3B hold for any arbitrarily shaped pulse of indicator injection, as well as for the impulse. They also apply when the injectate is infused at a constant rate, in which case \( A \) has the significance of equilibrium concentration in the atrium and \( B \) represents equilibrium concentration in the ventricle.

Three independent methods for measuring regurgitant flow in the continuous model are now indicated for different injection sites and sampling points.

1. The equation including \( s_1 \) (following equation 2A) can be solved for \( F_{BA} \) (atrial injection, ventricular sampling):

\[ F_{BA} = -\frac{V_A s_1^2}{F_P + s_1(V_A + V_B)} - F_P. \]  

(4A)

2. Equation 1B yields (simultaneous atrial and ventricular sampling):

\[ F_{BA} = \frac{V_R}{\alpha'(t) - \beta(t)} - F_P. \]  

(4B)

Both of the above methods require an additional means of determining \( V_R \) and/or \( V_A \) and \( F_P \).

3. Equation 3B can be solved for the fractional regurgitation (ratio of regurgitant to total flow) (ventricular injection with atrial and ventricular sampling):

\[ F_{BA}/F_T = A/B. \]  

(4C)

\( F_{BA} \) can be found directly from equations 3A and 3B:

\[ F_{BA} = \frac{A}{B} \frac{Q}{(B - A)}. \]  

(4D)

Solving equation 3A for the forward flow yields:

\[ F_P = Q/B. \]  

(4E)

Analysis Involving the Slope of Dilution Curves

The original Korner-Shillingford method for measuring regurgitation requires sampling only in the ventricle or in a major artery; a formula was derived which related regurgitation to the logarithmic slope of the tail of the dye curve, the central volume, and the cardiac output. Analysis of the mathematical model shows that the degree of regurgitation should not be significantly reflected in the slope of the curve. An electronic
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Simulated indicator-dilution curve with atrial volume as a variable. Atrial injection and ventricular sampling. Fixed parameters: \( V_B = 200 \) cc; \( F_F = 3 \) L./min.; \( F_{BA} = 2 \) L./min. Variable parameter: \( V_A = 100, 200, 300 \) cc.

An analog device (fig. 2) was constructed to display on the face of an oscilloscope voltage waveforms which resembled indicator concentration curves. Variations of the resistance and capacitance parameters of the simulator produced changes in the waveforms corresponding to variations of the flow and volume parameters of the mechanical system. Figures 3 through 5 illustrate that the shape of the curve is relatively insensitive to changes in regurgitation, whereas it is highly affected by the chamber volumes.

That methods relying on the details of the shape of the curve should work at all is mostly due to enlarged chamber volumes and low cardiac output generally accompanying severe cases of mitral regurgitation. This would explain the decreased peak concentration, delayed occurrence of the peak, and more gradual downslope of the concentration curves. However, the effect of increased chamber volume and reduced cardiac output on the shape of the curve is not the complete explanation; the Korner-Shillingford method can usually differentiate between mitral regurgitation and mitral stenosis, even when both are accompanied by comparable degrees of atrial enlargement and reduction of cardiac output. It has been suggested that mixing in the atrium is different in the two situations because of the presence or absence of a regurgitant jet.8

Mean Transit Times and Cardiac Chamber Volumes

It has been established by Hamilton14 and others that the volume of blood contained between the injection site and the sample site (and temporally equidistant points) can be determined by multiplying the cardiac output and the mean transit time (MTT, or \( t \)). This permits the determination of \( V_A \) and \( V_B \) needed for methods 1 and 2 of the previous paragraph. Hamilton techniques also show how \( F_F \) can be measured and will not be repeated here. The Hamilton measurements also theoretically permit the computation of regurgitant flows. The mean transit time is usually defined by one of the following equivalent formulations:

\[
\bar{t} = \frac{\Sigma tc(t)}{\Sigma c(t)}, \quad (5A)
\]

where \( t \) is measured from the time of injection and \( c(t) \) is the measured concentration curve at the sample site.

\[
\bar{t} = T + \frac{\Sigma tc(t)}{\Sigma c(t)}, \quad (5B)
\]

where \( T \), the appearance time, is the interval from injection to the time that indicator first appears at the sample site (\( \tau \) is measured from appearance time, \( \tau = t - T \)).

Chamber volumes of the continuous flow model can be calculated by the above method under certain conditions of flow. For atrial injection and ventricular sampling (from Appendix D),

\[
\bar{t}_b = \frac{1}{F_F} (V_A + V_B) \quad (6A)
\]

\[
F_F \times \bar{t}_b = V_A + V_B.
\]
This quantity is needed, along with \( V_B \), for the Kornor-Shillingford\(^2\) computation (i.e., equation 4A) as well as for some of the other techniques proposed. The product of mean transit time and cardiac output gives the volume of blood contained between the sample and injection sites, which is the combined volume of the atrium and ventricle. Notice that this mean transit time is independent of the regurgitant flow.

The ventricular volume \( V_B \) can theoretically be determined from the initial indicator concentration in the ventricle following injection into that chamber \( [V_B = Q/C(1)] \), where \( V_B \) is end-diastolic volume, \( Q \) is the quantity of indicator, \( C(1) \) is the end-diastolic concentration.

If sampling is done in the atrium, with atrial injection,

\[
\overline{\tau_a} = \frac{1}{F_F} (V_A + \frac{F_{RA}}{F_T} V_B) \quad (6B)
\]

\[ F_F \times \overline{\tau_a} = V_A + \frac{F_{RA}}{F_T} V_B. \]

Here the calculated volume is strongly dependent on regurgitant flow. If there is no regurgitation \( (F_{RA} = 0) \) and therefore no regurgitant volume, then the measured volume is simply the atrial volume; as far as the sampling instrument is concerned, we are dealing with one chamber only. What happens to the indicator after leaving the atrium, so long as none of it returns, is of no consequence. If the regurgitant flow is much greater than the forward cardiac output, there is so much transfer of fluid between the two chambers that, for all practical purposes, we have a one-chamber system the volume of which is the combined volume of the atrium and ventricle. This is what equation 6B shows. For \( F_{RA} \gg F_F \),

\[
\frac{F_{RA}}{F_T} \approx \frac{F_{RA}}{F_{RA}} = 1
\]

and

\[ F_F \times \overline{\tau_a} = V_A + V_B. \]

For ventricular injection and ventricular sampling, the mean transit time and calculated volume are:

\[
\overline{\nu}_b = \frac{1}{F_F} (V_B + \frac{F_{RA}}{F_T} V_A) \quad (6C)
\]

\[ F_F \times \overline{\nu}_b = V_B + \frac{F_{RA}}{F_T} V_A. \]

This is similar to the previous result, and can be explained in the same way.

For ventricular injection and atrial sampling,

\[
\overline{\nu}_a = \frac{V_A + V_B}{F_F} \quad (6D)
\]

\[ F_F \times \overline{\nu}_a = V_A + V_B. \]

Either equation 6B or 6C may be solved for \( F_{RA} \). Hence, for ventricular injection and ventricular sampling,

\[
F_{RA} = \frac{F_F (F_F \overline{\nu}_b - V_B)}{V_A + V_B - F_F \overline{\nu}_b}. \quad (7A)
\]

*Where there is no regurgitation, this result may appear to be startling, since there is no indicator concentration curve from the atrium. On the other hand, this leads also to an indeterminate mean transit time so that the Hamilton volume becomes the ratio of 0/0 which, when properly evaluated as a limit of \( F_{RA} \to 0 \), converges to 6D.*
Sampling sites in the atrium. (See Appendix F.)

For atrial injection and atrial sampling,

\[ F_{BA} = \frac{F_P (F_{TH} - V_A)}{V_A + V_B - F_{TH}}. \]  

(7B)

\[ V_A, V_B, \text{ and } F_{BA}/F_T \text{ can be found in terms of three mean transit times and just one volume measurement. Combining equations 6A and 6C,} \]

\[ F_{BA} = \frac{F_P t_b - V_B}{t_b - V_B}. \]  

(7C)

Another proposed method for determining the volume of blood contained in the largest chamber between the injection and sample sites does not require measurement of the MTT. The "Newman volume" is defined from the ratios of flow/slope where the slope is the asymptotic logarithmic derivative in equation 2A. In the case of the two-chamber system analyzed above,

\[ V = \frac{F_P}{S_1} - \frac{F_P (V_A + V_B)}{2V_AV_B} + \frac{\sqrt{F_T [F_P (V_A - V_B)^2 + F_{BA} (V_A + V_B)^2]}}{2V_AV_B}. \]

(7D)

(7E)

(7F)

We are indebted to the reviewer for pointing out this method.
where accurate measurements of volumes and mean transit times are impossible.

**Intermittent-Flow Model**

Analysis of the continuous-flow model was made primarily to show the effect of the flow and volume parameters on the shape of the concentration curves (equations 2A and 2B). Equations 4C, 4D, and 4E, which define regurgitant flow in terms of the integrated indicator concentration curves, can be rederived from a model of a system with intermittent flows and variable chamber volumes. Since such a model more closely approximates the physical action of the heart, insight should be gained into the mechanics of indicator flow.

Figure 1 serves as a diagram for this model, as well as for the continuous-flow model. $F_t$, $F_{BA}$, $F_{T}$ have the same significance in this model, with the exception that they represent amounts of fluid pumped per cycle, rather than volume per unit time. $V_A$ and $V_B$ represent end-diastolic volumes.

The flow conditions specified for the continuous-flow model apply to this model, with the exception that the mixing in the chambers need not be instantaneous. However, it is assumed that indicator in the ventricle becomes uniformly distributed prior to ventricular systole; similarly, indicator in the atrium becomes uniformly distributed before the beginning of ventricular filling. If this condition is fulfilled, the amount of indicator pumped out of a chamber on the $n^{th}$ systole is the concentration of indicator in that chamber multiplied by the amount of fluid expelled. The amount of indicator contained in a chamber just prior to systole is the indicator concentration multiplied by the end-diastolic volume.

Conservation of indicator in the system requires that the following difference equation be satisfied:

$$
[\beta(n + 1) - \beta(n - 1)] V_B = [\alpha(n) - \beta(n - 1)] F_T + Q(n) \quad (8A)
$$

$$
[\alpha(n + 2) - \alpha(n)] V_A = \beta(n - 1) F_{BA} - \alpha(n) F_T \quad (8B)
$$

where the argument of each concentration is referenced to systole of that chamber (see fig. 6); thus,

$$
\sigma(n) = \text{Concentration of indicator ejected from the atrium during the } n^{th} \text{ atrial systole.}
$$

$$
\beta(n + 1) = \text{Concentration of indicator ejected from the ventricle during the } (n + 1)^{st} \text{ ventricular systole.}
$$

$n = 0, 2, 4 \ldots$ indexes with each systole (both atrial and ventricular), the odd arguments occurring during ventricular systoles and the even during atrial systoles.

$Q(n) = \text{Amount of indicator added to the ventricle on the } n^{th} \text{ atrial systole. The } Q(n) \text{ need not be equal. Injection is made only during ventricular filling so that indicator can be well mixed by the start of systole.}$

If the number of injections is finite, the sum of indicator concentrations over all strokes will be finite.

Let

$$
\sum_{n=0}^{\infty} \sigma(n) = A.
$$

Let

$$
\sum_{n=0}^{\infty} \beta(n + 1) = B.
$$

$$
\sum_{n=0}^{\infty} Q(n) = Q.
$$

(Note that since every half-cycle is indexed, the $n$'s assume only even values in the summation.)

Performing the summations on equations 8A and 8B yields:

$$
0 = F_T(A - B) + Q. \quad (9A)
$$

$$
0 = F_{BA} B - F_T A. \quad (9B)
$$

Two independent methods can be derived for measuring regurgitant flow in the intermittent-flow model for ventricular injection:

1. Solving equation 8A for $F_{BA}$ yields a result analogous to equation 4B; assuming no indicator is added between the $n^{th}$ and $(n + 1)^{st}$ systole, from simultaneous atrial and ventricular sampling,

$$
F_{BA} = \left[\frac{\beta(n + 1) - \beta(n - 1)}{\alpha(n) - \beta(n - 1)}\right] V_B - F_T. \quad (10A)
$$

2. Regurgitant flow can be related to the sum-of-concentrations here just as it was related to the integrated concentration curves in the continuous-flow model. From equations...
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AORTA

ATRIUM SITE 2

Figure F-5
Indicator curves following single injection. (See Appendix F.)

9A and 9B, with atrial and ventricular sampling,

\[ \frac{F_{BA}}{F_T} = \frac{A}{B} \quad (10B) \]

\[ F_{BA} = \frac{A}{B} \left( \frac{Q}{B-A} \right) \quad (10C) \]

\[ F_{BA} = \frac{Q}{B-A} - F_F \quad (10D) \]

\[ F_F = \frac{Q}{B} \quad (10E) \]

It can be shown that the preceding three equations also apply to the case of periodic injection, in which case \( A \) and \( B \) refer to equilibrium concentrations. Under these circumstances, \( Q \) is the amount of indicator added each cycle.

Consideration of the details of the initial segments of the dilution curves provides another approach to the quantification of regurgitation. Solution of the difference equations 8A and 8B for a ventricular injection of quantity \( Q \) at \( n = 0 \), yields:

\[ a(0) = 0 \quad \alpha(2) = \frac{QF_{BA}}{V_B V_A} \]

\[ \beta(1) = \frac{Q}{V_B} \quad \beta(3) = \frac{Q}{V_B} \left( 1 + \frac{F_T}{V_B} \left( \frac{F_{BA}}{V_A} - 1 \right) \right) \]

Regurgitation can be computed from atrial sampling and a knowledge of chamber volumes:

\[ F_{BA} = \frac{V_B V_A \cdot \alpha(2)}{Q} \quad (11A) \]

or from ventricular sampling,

\[ F_{BA} = \frac{(V_A - F_F) \pm \sqrt{(F_F + V_A)^2 + 4V_A V_B \left( \beta(3)/\beta(1) - 1 \right)}}{2} \quad (11B) \]

Summary of Theory

A number of methods for computing mitral regurgitation, not all of them independent, have been derived for a well-defined mathematical model. For convenience, the solutions are listed below. They are grouped according to the type of instrumentation that would be required for each. Where the results of the continuous-flow analysis and the intermittent flow analysis are analogous, the latter are presented.

1. Atrial injection, ventricular sampling, measurement of asymptotic ventricular loga...
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arithmic derivatives, atrial and ventricular volumes, and cardiac output \((F_P)\):

\[
F_{BA} = -\frac{V_AV_B s_1^2}{F_P + s_1(V_A + V_B)} - F_P. \tag{4A}
\]

2. Ventricular injection, atrial sampling, measurement of both volumes, and cardiac output:

\[
F_{BA} = \frac{V_AV_B a(2)}{Q} \tag{11A}
\]

\[
F_{BA} = \frac{(V_A - F_P) \pm \sqrt{(F_F + V_A)^2 + 4V_AV_B}}{2} \tag{11B}
\]

3. Injection into one chamber, sampling in the other, measurement of mean transit time, both volumes, and cardiac output:

\[
F_{BA} = \frac{F_P(F_P V_B - V_B)}{V_A + V_B - F_P t_b} \tag{7A}
\]

\[
F_{BA} = \frac{F_P (F_P t_b - V_A)}{V_A + V_B - F_P t_b}. \tag{7B}
\]

4. Ventricular sampling, atrial and ventricular injection, two mean transit times, measurement of ventricular volume, and cardiac output:

\[
F_{BA} = \frac{F_P t_b - V_B}{t_b - t'_b}. \tag{8A}
\]

5. Sampling in both chambers, measurement of ventricular volume, injection into either atrium or ventricle, and cardiac output:

\[
F_{BA} = \frac{\beta(n + 1) - \beta(n - 1)}{\alpha(n) - \beta(n - 1)} V_B - F_F. \tag{10A}
\]

6. Sampling in both chambers, no volume measurements, injection into ventricle:

\[
\frac{F_{BA}}{F_P} = A/B \tag{10B}
\]

\[
F_{BA} = \frac{A}{B} \frac{Q}{(B - A)} \tag{10C}
\]

\[
F_{BA} = \frac{Q}{B - A} - F_F. \tag{10D}
\]

7. Two consecutive trials: injecting into the atrium and sampling in both chambers on one trial; ventricular injection and ventricular sampling on the second:

\[
\frac{F_{BA}}{F_P} = \frac{t_b - t_a - t_b}{t_b}. \tag{10E}
\]

**Experiments on a Mechanical Model**

This section is concerned with the experimental evaluation of the predicted results and presents data obtained from a mechanical model designed to simulate the flow pattern in the atrium and ventricle.\(^*\) Use of a model of this kind is not a substitute for the biological system but offers the advantages that (a) the important parameters are readily controlled or measured, and calculated results that deviate from these parameters are more easily detected; and (b) the instrumentation system can be conveniently developed and tested.

While the model has some utility in establishing reasons for poor measurement, success in the model is no guarantee of physiological success. The rigidity of the walls and the failure to duplicate the exact dynamics of the regurgitant jet suggest that model results be treated with suitable caution.

Reliable measurements of mitral regurgitation, using the thermal indicator-dilution technique, were generally obtained for both single injection and periodic injection experiments on the model with sampling sites located at the center of the atrium. While only a few of the methods were tried, model measurements disclosed potentially significant difficulties in measuring technique. At sampling sites in the region of the valve, where the indicator concentration is strongly dependent on the local character of the regurgitant flow, the results obtained varied widely between successive experiments and did not yield any useful measure of the regurgitation. Some residual variations in the experimental parameters prevented truly repeatable results from being obtained, but these fluctuations were not of sufficient magnitude to explain the unsatisfactory nature of the observations using sampling sites near the valve.

\(^*\)Details of the experiment are given in Appendix F.
Summary

Methods for quantifying mitral regurgitation that require the measurement only of the area enclosed by the indicator-dilution curves offer the advantage of being computationally simpler than the others. Furthermore, distortions in the shape of the curve will not necessarily induce significant error in the area enclosed by the curve. Since such methods require sampling from the atrium as well as from the ventricle, or proximal aorta, they will be successful only if meaningful samples of indicator concentration can be obtained from these chambers.

The question remains to be answered: Is the mixing in the cardiac chambers sufficient to allow meaningful sampling in both atrium and ventricle? A review of the literature on this subject has been inconclusive.\(^{12-17}\) We are not aware of any experiments in which all of the conditions affecting cardiac chamber mixing have been controlled without seriously disturbing normal cardiac physiology. Such an experiment should control the nature of injection (i.e., one or many successive pulses), the number and placement of the orifices at the tip of the injection catheter, and the timing of the injection with the cardiac cycle.

Experiments indicate that the optimum mixing conditions exist at the beginning of ventricular filling and that injection should be timed to coincide with this point in the cycle. It is of interest to note that, in the dye curve experiments by Sinclair et al.\(^{18}\) in which animals were used, the time at which injections were made was found to be unimportant. This important difference between the mixing characteristics of the mechanical model and an animal heart illustrates the difficulties encountered in the application of model results and observations to the human heart. It seems reasonable to conjecture, however, that the well-established mixing properties of flows through valves and orifices in rigid systems will be enhanced in the deformable wall situation encountered in the heart. Further experiments using the indicator-dilution technique on both normal and abnormal hearts are evidently required to determine the nature and extent of the dependence of measurement reliability on the sampling site location.

Acknowledgment

The authors acknowledge their indebtedness to Dr. Lewis Dexter of the Peter Bent Brigham Hospital and his past and present associates for their patient teaching, critical evaluation of the models proposed, and generous applications of experience.

Appendices

Appendix A. List of Symbols Used in this Paper

\[
\begin{align*}
F_r & = \text{Forward flow (cardiac output).} \\
F_{RA} & = \text{Regurgitant flow, from ventricle to atrium.} \\
F_v & = \text{Total ventricular flow, the sum of forward and regurgitant flows.} \\
\alpha(t) & = \text{Indicator concentration in the atrium, applied to the continuous-flow model, at time } t. \\
\alpha(n) & = \text{Indicator concentration in the atrium, applied to the intermittent-flow model, at the } n^{th} \text{ stroke.} \\
\beta(t) & = \text{Indicator concentration in the ventricle, applied to the continuous-flow model, at time } t. \\
\beta(n + 1) & = \text{Indicator concentration in the ventricle, applied to the intermittent-flow model, at the } (n + 1)^{st} \text{ stroke.} \\
\beta'(t) & = \text{Ventricular concentration after ventricular injection for continuous-flow model at time } t. \\
V_a & = \text{End-diastolic atrial volume.} \\
V_n & = \text{End-diastolic ventricular volume.} \\
s & = \text{Exponent of the exponential decay function.} \\
A & = \text{Area under the atrial concentration curve, applied to the continuous-flow model; sum of atrial concentrations, applied to the intermittent-flow model.} \\
B & = \text{Area under the ventricular concentration curve; sum of ventricular concentrations.} \\
Q & = \text{Quantity of indicator injected into the flow system.} \\
\bar{t}_a & = \text{Mean transit time: atrial injection, atrial sampling.} \\
\bar{t}_v & = \text{Mean transit time: ventricular injection, ventricular sampling.} \\
\bar{t}_a & = \text{Mean transit time: atrial injection, ventricular sampling.} \\
\bar{t}_v & = \text{Mean transit time: ventricular injection, atrial sampling.} \\
\end{align*}
\]

Appendix B. Solution to the Differential Equations of Flow

From equations 1,

\[
\frac{d\alpha(t)}{dt} = \frac{F_{RA} \beta(t) - F_v \alpha(t)}{V_a} \quad (B-1)
\]

\[
\frac{d\beta(t)}{dt} = \frac{F_v \alpha(t) - F_v \beta(t)}{V_n}
\]
Transforming equations 1 by Laplace transformation methods yields:

\[ sA(s) = \frac{F_{BA} B(s) - F_T A(s)}{V_A} + \alpha(0) \]  
\[ sB(s) = \frac{F_T [A(s) - B(s)]}{V_B} + \beta(0), \]

where \( \alpha(0) \) is the concentration of indicator in the atrium at \( t = 0 \), and \( \beta(0) \) is the concentration of indicator in the ventricle at \( t = 0 \).

Rearranging equations B-2 yields:

\[ B(s) = \left[ \frac{F_T V_A \alpha(0)}{V_A} + V_A V_B \beta(0) \right] \frac{s + F_T/V_A}{(s-s_2) (s-s_1)} \]
\[ \frac{A(s)}{V_A V_B} = \frac{s + F_T/V_B}{(s-s_2) (s-s_1)} \alpha(0) + F_{BA} V_B \beta(0), \]

where

\[ s_1 = -\sigma + \delta = \frac{F_T (V_A + V_B)}{2V_A V_B} \]
\[ s_2 = -\sigma - \delta = \frac{F_T (V_A + V_B)}{2V_A V_B} \]

There is no indicator in the system until injection is made into either the atrium or the ventricle at \( t = 0 \).

Following injection of an impulse of indicator into the atrium, \( \alpha(0) = Q/V_A \) and \( \beta(0) = 0 \),

\[ A(s) = \frac{\left( (s + F_T/V_B) \right) Q}{V_A (s-s_1) (s-s_2)} \]
\[ B(s) = \frac{F_T Q}{V_A V_B (s-s_1) (s-s_2)} \]

\[ \alpha(t) = \frac{Q}{28V_A} \left( \left( s_1 + F_T/V_A \right) \exp(s_1 t) - (s_2 + F_T/V_B) \exp(s_2 t) \right) \]
\[ \beta(t) = \frac{F_T Q}{28V_B} \left( \exp(s_1 t) - \exp(s_2 t) \right). \]

For ventricular injection of an impulse of indicator, \( \alpha(0) = 0 \) and \( \beta(0) = Q/V_B \),

\[ A(s) = \frac{F_{BA} Q}{V_A V_B (s-s_1) (s-s_2)} \]
\[ B(s) = \frac{Q \left( s + F_T/V_B \right)}{V_B (s-s_1) (s-s_2)} \]

\[ \alpha'(t) = \frac{Q F_{BA}}{2V_A V_B} \left[ \exp(s_1 t) - \exp(s_2 t) \right] \]
\[ \beta'(t) = \frac{Q}{28V_B} \left( (K + \delta) \exp(s_1 t) + (-K + \delta) \exp(s_2 t) \right), \]

where

\[ K = \frac{F_T (V_B - V_A)}{2V_A V_B}. \]
Appendix D. Mean Transit Times and Calculated Volumes

Mean transit time \( \bar{t} \) is defined as

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

where \( c(t) \) is the concentration at the sample site. Time is measured from injection.

From Laplace transform considerations, we know

\[
\int_0^\infty t c(t) \, dt = \lim_{s \to 0} -\frac{d}{ds} \mathcal{L}^{-1}(C(s)),
\]

where \( \mathcal{L}^{-1} \) is the inverse Laplace transform of \( c(t) \).

The mean transit time of the atrial curve (\( t_a \)) is

\[
\frac{\int_0^\infty t \alpha(t) \, dt}{\int_0^\infty \alpha(t) \, dt} = \lim_{s \to 0} -\frac{d}{ds} \mathcal{A}(s) \quad \text{as} \quad s \to 0
\]

Similarly, the mean transit time of the ventricular curve (\( t_v \)) is

\[
\frac{\int_0^\infty t \beta(t) \, dt}{\int_0^\infty \beta(t) \, dt} = \lim_{s \to 0} -\frac{d}{ds} \mathcal{B}(s) \quad \text{as} \quad s \to 0
\]

From equations B-3, it can be shown that

\[
-\frac{d}{ds} \mathcal{A}(s) = \frac{2s - s_1 - s_2}{(s-s_1)(s-s_2)} + \frac{V_A}{s} \alpha(0)
\]

\[
-\frac{d}{ds} \mathcal{B}(s) = \frac{2s - s_1 - s_2}{(s-s_1)(s-s_2)} + \frac{V_B}{s} \beta(0)
\]

For ventricular injection of an impulse of indicator,

\[
\begin{align*}
\bar{t}'_a &= -\frac{s_1 - s_2}{s_1 s_2} + 0 \\
\frac{V_A}{F_p} + \frac{V_B}{F_p}
\end{align*}
\]

\[
\begin{align*}
\bar{t}'_b &= \frac{s_1 - s_2}{s_1 s_2} - \frac{V_A}{F_T} \\
&= \frac{1}{F_T} \left( \frac{V_B}{F_T} + \frac{F_{PA}}{F_T} V_B \right)
\end{align*}
\]

Appendix E. Relation of Indicator Concentration to Volume Flow

Consider the flow of indicator through a valve. The assumption is made that the indicator concentration is uniform across the face of the valve. This is not unreasonable if the valvular orifice is small compared to the total surface area of the source chamber.

Let \( c(t) \) = Indicator concentration at the valve.

\( f(t) \) = Rate of fluid flow through the valve.

\( t_1 \) = Time at which flow commences.

\( t_2 \) = Time at which flow ceases.

\( \frac{dQ}{dt} \) = Rate of indicator flow across the valve.

\( F \) = Total amount of fluid pumped during the period \( t_2 - t_1 \).

\( Q \) = Total amount of indicator carried through the valve during the period \( t_2 - t_1 \).

\[
F = \int_{t_1}^{t_2} f(t) \, dt.
\]

\[
Q = \int_{t_1}^{t_2} c(t) \cdot f(t) \, dt.
\]

In the analysis of the mathematical models, it is stated that the amount of indicator pumped out of a chamber during systole equals the amount of fluid pumped times the concentration of indicator in that chamber. The indicator is assumed to be distributed uniformly throughout the chamber; the concentration is assumed to remain constant during expulsion of fluid. An “average” concentration \( \bar{c} \) shall be defined from the above relationships such that

\[
Q = \bar{c} \times F_p = \int_{t_1}^{t_2} c(t) \cdot f(t) \, dt.
\]

Unless \( \bar{c} \) can be obtained from measurements of \( c(t) \), measurements of flow by indicator techniques will be unreliable, and it is not obvious that \( \bar{c} \) can be determined unless either \( c(t) \) or \( f(t) \) is removable from the integrand.
If the flow rate is constant during the period $t_1 - t_2$,

$$\bar{v} = \frac{Q}{F_k} = \frac{\int_{t_1}^{t_2} f(t) \, dt}{t_2 - t_1}$$

In this case, $\bar{v}$ is the average value of $c(t)$ between times $t_1$ and $t_2$. However, in the functioning heart, $f(t)$ continuously varies during systole. Only if mixing in the cardiac chambers has been complete will the indicator concentration at the valve be constant ($\bar{c}$) during systole.

Thus, $\bar{v}$ could in this case be measured regardless of the form of $f(t)$, but the necessity of chamber mixing has not been avoided.

Appendix F. Experiments with a Mechanical Model

Materials and Methods

The model and its associated flow system are shown schematically in figures F-1 and F-2, respectively. The two chambers representing the "atrium" and "ventricle" were fabricated principally from brass; they were rectangular in shape, being roughly 4 inches high, 3 inches wide, and 3 inches deep. A movable piston extended into each chamber to simulate the expansion and contraction of the heart walls and also to provide the force required to pump water through the system. The two pistons were driven by a single electric motor through a system of belts and pulleys, and provision was made for the independent adjustment of their pumping volumes.

Rubber flap valves were appropriately placed to ensure that there was a net flow of water in the desired direction. A perfect valve was installed at the outlet ("aortic" valve) to prevent backflow into the ventricle. The amount of mitral regurgitation, or backflow from ventricle to atrium, could be partly controlled by cutting holes of various sizes in the flap valve between the two chambers. The inlet valve was always operated under regurgitant flow conditions.

A relatively constant backpressure was provided by an outlet reservoir located 30 inches above the pumping chambers. This reservoir emptied into a sink, which also served as the inlet reservoir. Recirculation during the experiment could be prevented by draining the outlet reservoir into a separate vessel while measurements were being made.

Good mixing in the ventricle was assured by the auxiliary mixer indicated in figure F-1, but mixing in the atrium was not similarly aided for reasons given later.

Ventricular concentrations were measured in the outlet tube about an inch beyond the aortic valve rather than in the ventricle itself. Two sampling sites were provided for the atrium as shown in figure F-3, one in the middle of the chamber (site 1), and the other near the mitral valve (site 2). In all experiments the indicator was injected into the ventricle.

Heat (i.e., an induced temperature change) was used as the indicator. Considerations in support of this procedure are that the thermal transducer has a relatively small time constant and can be placed directly in the flowing fluid, thus minimizing distortion of the resulting indicator curves by the sampling system. Cardiac output has been successfully determined by Goodyear et al.\textsuperscript{10} using a thermistor as the temperature sensing element for the thermal dilution method. In the experiments described here, the thermal transducers were Glenite 32CB2 thermistors.

The two sampling thermistors were connected to separate electrical channels. Each thermistor formed one arm of a modified Wheatstone bridge which was excited by a 5 kc./sec. sine wave oscillator. The operating voltage was chosen to be at a level low enough to ensure negligible self-heating due to power dissipation within the thermistor. The bridge output signal was amplified by a high gain A.C. amplifier, rectified and fed into the D.C. amplifier of a pen recorder. The thermal probes had time constants\textsuperscript{*} of about 0.4 seconds.

The "indicator" (hot water) was either injected as a bolus of 5 to 10 cc. or was added periodically at a rate of 48 pulses per minute with an average flow rate of 25 cc. per minute. The single injection was performed manually, and the repeated injections were made by a Process and Instruments model 2 pump.

Prior to each experiment, the following steps were taken in sequence: (1) The size of the regurgitant orifice of the mitral valve was adjusted. (2) The atrial thermistor was placed at the de-

\textsuperscript{*}The time constant was measured by suddenly plunging a probe into a water bath at a temperature slightly different from that of the surrounding air. The time constant is defined as the time it takes a thermistor to register a temperature change of $(1-1/e)\Delta T$ when the thermistor is subjected to a temperature change of $\Delta T$.  

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sired sample site. (3) The pumping volumes of the atrium and ventricle were adjusted. (4) The water in the inlet reservoir was allowed to reach thermal equilibrium with the surrounding air to eliminate any subsequent drift in baseline. (5) The pump rate was adjusted. (6) The auxiliary mixer in the ventricle was turned on.

The forward flow and total ventricular flow were measured directly during each experiment to provide data with which the thermal-dilution measurements could be compared. The total ventricular flow (the pumping volume of the ventricle) could readily be determined by measuring the amount of piston travel. The forward flow was determined by weighing the water pumped out of the system in a specified time interval, and this measurement was divided by the pumping rate to determine the output in terms of cubic centimeters per cycle.

One quantity of interest in defining regurgitation is the ratio \( R = \frac{F_{RA}}{F_T} \), given by equation 4C. Although the quantities \( A \) and \( B \), from which \( R \) is calculated, have been defined as the sums of the indicator concentrations, they may also be defined as the areas enclosed by the indicator curves provided the pump rate remains constant during a given experiment. In making the calculations reported here, it was found more convenient to measure these areas rather than to sum the concentrations. Since the indicator concentration sampling system associated with the ventricle generally had a different sensitivity from that associated with the atrium, it was necessary to normalize the areas of the two curves to the same scale. The normalized area was calculated from the following formula:

\[
A = A' \times \frac{1}{k} \times \frac{1}{dR/dT},
\]

where \( A \) = the normalized area,

\( A' \) = the actual area enclosed by the curve as measured with a planimeter,

\( k \) = the calibration of the writing arm in units of millimeter of deflection per ohm of resistance change of a bridge arm,

\( dR/dT \) = the sensitivity of the thermistor* in ohms per degree of temperature change.

**Results**

Figures F-4 and F-5 show typical sets of curves obtained following a single-bolus injection.

*The resistance of the thermistor is related to temperature in an exponential form; however, for very small changes in temperature (as encountered in experiments), the resistance change with temperature may be approximated by a linear relation. The slope of the line \( dR/dT \) is a function of the base operating temperature.

In figure F-4, the atrial curve was recorded from the middle of the chamber (site 1), and in figure F-5 atrial concentration was sampled near the valve (site 2). Smooth curves were drawn through the original tracings as shown, and the areas under these curves were used for computations. Two alternative \( A/B \) ratios were computed from each set of curves of the type given in figure F-5. The ratio \( A_1/B \) is that obtained from the area under the lower curve only, whereas \( A_2/B \) is given by the average of the areas under both lower and upper curves. The oscillations in the atrial curve of figure F-5 are to be expected, since the thermistor was situated in the stream of the regurgitant jet.

Figure F-6 shows a pair of curves recorded during repeated injection. The atrial curve was recorded from site 1. Ideally, the concentration curves should rise asymptotically to steady-state values. A horizontal line was drawn through the relatively flat portion of each curve to average out the fluctuations.

Table F-1 lists the results of the single-injection experiments and table F-2 the corresponding results of the periodic-injection experiments. The \( R_m \) column shows the ratio of regurgitant to total flow as measured directly on the model. The \( R_c \) column displays the ratios calculated from the thermal-dilution curves. Where there are two entries in the \( R_c \) column for a single experiment: the upper value represents \( A_1/B \); the lower value is \( A_2/B \). The data recorded from each sample site are grouped together; and within each grouping, the experiments are listed in order of increasing values of \( R_m \).

An acceptable result may be defined as one in which the calculated value of \( R \) is within 20 percent of the measured value. Experiments 1 through 5, which involved sampling at site 1, following single injection, gave results falling into this category. and one member of each pair of results of experiments 6 through 13 is also acceptable. In the latter set, five of the acceptable experiments (6, 7, 8, 9, 12) are based on use of the ratio \( A_1/B \), while the remaining three (10, 11, 13) require selection of the \( A_2/B \) ratio results. Three out of the four periodic-injection experiments during which atrial concentrations were recorded from site 1 (15, 16, 17) meet the required standards, while only two (experiments 22 and 24) of the nine curves sampled at site 2 are acceptable.

Notice that, generally speaking, the percentage error is largest for small values of \( R \). This is to be expected, since for small \( R \) the atrial concentrations are relatively low, making more difficult an accurate determination of the area under the curve.
The figure immediately beneath is calculated from the average area of the two smooth curves. The figure immediately beneath is calculated from the average area of the two smooth curves.

Discussion

These experiments reveal that the reliability of the two-chamber sampling method for measuring regurgitant flow is strongly dependent on the location of the atrial sample site. This conclusion has also been arrived at by Lacy et al., using a model of somewhat different construction and instrumentation, and by Sinclair et al. as a result of dye-curve experiments with animals. Sampling in the immediate vicinity of the valve is at best of questionable value, as concentrations measured in making some of the calculations. Some of the tracings obtained from site 2 in the atrium, such as the one shown in figure F-7, were very difficult to approximate by smooth curves. Drawing the smooth curve in a different way could make a noticeable difference in the calculated area. It would be extremely difficult to devise a formula for making consistent approximations to such curves.

Precise reproducibility of experimental data could not be obtained due to the nature of the apparatus. The problems involved in regulating the various parameters responsible for this difficulty are discussed in the following paragraphs.

Pumping Volumes. The ventricular pumping volume was controlled to within 2 per cent of 148 cc. per cycle during all experiments. In all but eight of the experiments atrial pumping was not present, and in the cases where this was allowed, it was a small fraction of the chamber volume. (Both atrium and ventricle had diastolic volumes of about 700 cc.) Atrial pumping was found to have no detectable effect on the results of the experiments.

Rate. The rate was adjusted with the aid of a variable ratio autotransformer which supplied the drive motor. This rate was sometimes observed to change suddenly, due to a variation in line voltage. For each experiment, the rate was determined by timing the period consumed by 20 cycles of the pump. This average rate measurement was accurate to 1 or 2 per cent. No check was kept on the cycle-to-cycle variation of the rate but data obtained when the pump rate changed suddenly were discarded.

Regurgitant Orifice. The regurgitant orifice was adjusted in the following manner: A hole, larger in diameter than the desired orifice, was punched in the flap, and a washer with an inner diameter of the desired size was then glued over the hole. The orifice was, therefore, constant from best to best. (For most experiments, the orifice was 5 mm. in diameter.) Some fluid leaked back around the edges of the valve as the valve was closing, but no attempt was made to measure this effect.

Forward and Regurgitant Flows. These parameters were very difficult to control closely. The ratio of regurgitant to forward flow depended on the pressure pattern, which in turn was a function of the pumping volumes, pump rate, and regurgi-
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A variation in any one of these parameters alone could produce a variation in $F_F$ (and hence in $F_{F_B}$). Although the average flow could be determined to be steady, there was no provision for measuring the cycle-to-cycle flow.

Injection. Attempts were made to confine the single-pulse injections to the filling period of the ventricle so that the water in the chamber would be at a uniform temperature during the emptying phase. This was not always successful, as indicated with pumping action. When injection occurred steadily throughout the operation of the model and held exactly to that at which the repeated injections were delivered (48 pulses per minute). Consequently, there was a continual drift in the phasing between indicator injection and pump action.

The procedure of promoting mixing in the ventricle only simulates the physiological situation in which it is established that pumping action produces a thorough mixing of indicator in the ventricle than in the atrium. It was not possible to keep the experimental parameters constant throughout the operation of the model and evidence of this is seen in figure F-8, which shows a result typical of some of the periodic injection experiments. Notice that the "equilibrium concentrations" in the atrium and ventricle are not steady levels, but change slowly with time at roughly 1 cycle per minute. This drift may have occurred because injection was not synchronized with pumping action. When injection occurred during ventricular filling, the indicator had a chance to mix reasonably well with the ventricular contents before being pumped out. When injection occurred during contraction, some of the indicator was evidently expelled before the auxiliary mixer was able to function on it.

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Circ Res. 1961;9:1109-1125
doi: 10.1161/01.RES.9.5.1109

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

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