Inlet and Intrachamber Concentration Distributions in Tracer Studies of the Canine Central Circulation and Their Relation to the Isotope Dilution Residue Function

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SUMMARY We analyzed the isotope dilution residue function from a single cardiac chamber for an arbitrary inlet distribution of tracer and arbitrary mixing within the chamber, and established a general relationship between cardiac output and the chamber residue function. In our experiments, we made simultaneous temperature measurements in three left ventricular chamber subregions of the dog subjected to left and right atrial injections of chilled saline. Flow-proportional tracer labeling always occurred at the left ventricular inlet when injection was into the right atrium. This state almost never obtained, however, with direct left atrial injection, although it was approximated most closely when multiple side hole catheters were used. We also demonstrated that imperfect tracer mixing in the normal ventricle can lead to significant regional temperature inequalities during tracer passage. These inequalities are more pronounced in the ventricle with compromised function, but in both normal and compromised ventricles they are minimal several beats after tracer concentration peaks if injection is into the right atrium.

INDICATOR dilution techniques for measurement of cardiac output were introduced by Stewart in 1898, and over the past 80 years have been extended by others to the measurement of transit volume and ejection fraction by both in-vivo concentration sampling, and external detection of γ-emitting tracers (Hamilton et al., 1931; Newman et al., 1951; Holt, 1956; Holt and Allenworth, 1957; Rapaport et al., 1962; Ishii and MacIntyre, 1971; Schelbert et al., 1975). The theoretical bases for these techniques have been well-defined by Stephenson (1948), Meier and Zierler (1954), Gonzalez-Fernandez (1962), Zierler (1962, 1965), Bassingthwaighte and Holloway (1976), and Cottrall (1977). Investigators have long been concerned with the problem of imperfect tracer mixing in chambers of the heart and the resulting effect on parameter estimation. This concern has assumed current clinical significance with the development and use of radioisotope dilution techniques for the dynamic study of heart function (Pierson et al., 1977).

Although several studies report evidence of imperfect mixing in the dog left ventricle (Irisawa et al., 1960; Swan and Beck, 1960; Rolett et al., 1964; Petre and Avasthey, 1968; Pavek et al., 1970; Boyle, 1974), little attention has been paid to the effects of injection site and catheter tip configuration on the distribution of tracer at the left ventricular inlet or to the effect of compromised ventricular function on intrachamber mixing. Theoretical treatments have considered tracer distributions in vascular beds and tubes with laminar flow normal to a measurement plane (e.g., Gonzalez-Fernandez, 1962; Zierler, 1962), and explicit relationships have been developed for flow-proportional and uniform cross-sectional tracer labeling at the inlet plane and for mean flow and mean cross-sectional concentration sampling at the measurement plane. The analysis of isotope dilution residue functions from a single cardiac chamber in terms of an arbitrary inlet distribution of tracer and arbitrary mixing within the chamber has not been well defined. In this situation the residue function includes contributions from well and poorly mixed regions, and tracer can recirculate within chamber subregions.

The purpose of this paper is (1) to provide further insight into the analysis of isotope dilution residue functions from a single chamber with an arbitrary inlet distribution of tracer, and arbitrary mixing within the chamber, (2) to demonstrate the effect of injection site and catheter tip configuration on the inlet tracer distribution, and (3) to demonstrate the effect of compromised ventricular function on intrachamber mixing.

Theory

Tracer mixing in a chamber must be evaluated in terms of the inlet tracer distribution as well as intrinsic mixing properties of the system. The inlet tracer distribution is affected by prior passage
through a mixing chamber, catheter design, injection characteristics, and flow patterns (Andres et al., 1954), and intrachamber mixing is determined by intrachamber convective mass transport, which is affected by flow-rate and anatomical factors.

In the analysis presented herein, the left ventricle is modeled as a single chamber with arbitrary but time-independent internal mixing properties. The system is assumed linear in a mathematical sense with constant flow and volume, and an expression is developed for the integral of the concentration-time curve at any location within the chamber in terms of the spatial distribution of tracer in the inlet stream, and intrachamber mixing. It is proved that all such integrals are identical if the inlet distribution of tracer is proportional to flow (flow-proportional labeling). Based on this proof, it is demonstrated that calculation of cardiac output from isotope dilution and ventricular residue detection is correct if (1) tracer labeling at the chamber inlet is flow proportional or (2) mixing is perfect within the chamber.

Consider a constant-volume (V) chamber (the system) composed of N constant-volume, perfectly mixed subcompartments interconnected in an arbitrary way by convective and turbulent transport [for a general discussion of systems of this type see, for example, Bergner (1961a, 1961b)]. Further, consider an inlet stream with constant total flow Q made up of M substreams each with uniform velocity $v_j$, and flow $Q_j$. Each subcompartment receives fluid either directly from this inlet stream or via a path involving other subcompartments. We postulate an arbitrary distribution of injected tracer at the inlet such that the tracer flow-rate associated with substreams $j$ is $i_j(t)$ (g/sec), and assume the entire system to be linear with arbitrary but time-independent internal mixing properties. We also postulate stationarity and no recirculation of tracer once it leaves the system. Let $C_{ji}^{in}(t)$ be the tracer input function associated with substream $j$, and let $C_{ij}(t)$, $C_{ij}^*(t)$, and $C_{ij}^*(t)$, respectively, represent the response of the $i$th subcompartment when $C_{ij}^{in}(t)$ is an arbitrary function, a unit step, and a unit impulse, and $C_{ij}^{in}(t) = 0$ for $j = 1, 2, \ldots (j - 1), (j + 1), (j + 2), \ldots M$.

It can be shown for a linear system that if two inputs are related by a linear operator (e.g., differential operator), the outputs will be similarly related (Himmelblau and Bischoff, 1968). Since the first derivative of a unit step is an impulse, it follows that the integral of the first derivative of the step response in the $i$th subcompartment is equal to the integral of the impulse response. That is

$$\int_0^\infty (dC_{ij}^*(t)/dt) dt = C_{ij}^*(t) |_\delta = \int_0^\infty C_{ij}(t) dt.$$

Since any arbitrary input can be approximated as a series of impulses, and the overall subcompartment response obtained by summing individual impulse responses (Himmelblau and Bischoff, 1968), it follows that

$$\int_0^\infty C_{ij}(t) dt = K \cdot B_{ij}$$

where $K$ is a constant, and also that

$$\int_0^\infty C_{ij}(t) dt = K \cdot B_{ij} = (I_j/Q_j)B_{ij}$$

where $I_j = \int_0^\infty i_j(t) dt.$

Since the system is linear, the subcompartment response to simultaneous tracer inputs in all $j$ substreams is identical to the sum of the responses to all such inputs considered separately. Thus

$$\int_0^\infty C_i(t) dt = \sum_{j=1}^M \int_0^\infty C_{ij}(t) dt = \sum_{j=1}^M (I_j/Q_j)B_{ij}$$

where $C_i(t)$ is the time-dependent concentration that would be measured by a detector in subcompartment $i$. The ratio $I_j/Q_j$ is determined by the distribution of injected tracer in the inlet stream, and $B_{ij}$ by intrinsic mixing within the chamber.

**Case I: Flow-Proportional Tracer Labeling at the Inlet**

For the case of flow-proportional labeling, as discussed, for example, by Gonzalez-Fernandez (1962), all $i_j(t)/Q_j$ are identical. It then follows that all $I_j/Q_j$ must be identical and in fact equal to $I/Q$, where $I$ is the total tracer injected and $Q$ is the total flow through the system. Equation 6 now becomes

$$\int_0^\infty C_i(t) dt = (I/Q) \sum_{j=1}^M B_{ij} = I/Q.$$  

We define this condition as perfect mixing of tracer in the inlet stream.

**Case II: Perfect Mixing within the Chamber**

For a perfectly mixed chamber, the fraction of flow to subcompartment $i$ that derives from substream $j$ is equal to $Q_i/Q$, and

$$\int_0^\infty C_i(t) dt = \sum_{j=1}^M I_j/Q_i B_{ij} = \sum_{j=1}^M I_j/Q = I/Q.$$  

multiplied by the fraction of flow to that subcompartment that derives from substream $j$. If we designate this fraction as $B_{ij}$, we can write

$$\int_0^\infty C_{ij}(t) dt = 1 \cdot B_{ij}.$$

Since any arbitrary input can be approximated as a series of impulses, and the overall subcompartment response obtained by summing individual impulse responses (Himmelblau and Bischoff, 1968), it follows that

$$\int_0^\infty C_{ij}(t) dt = K \cdot B_{ij}$$

where $K$ is a constant, and also that

$$\int_0^\infty C_{ij}(t) dt = K \cdot B_{ij} = (I_j/Q_j)B_{ij}$$

where $I_j = \int_0^\infty i_j(t) dt.$

Since the system is linear, the subcompartment response to simultaneous tracer inputs in all $j$ substreams is identical to the sum of the responses to all such inputs considered separately. Thus

$$\int_0^\infty C_i(t) dt = \sum_{j=1}^M \int_0^\infty C_{ij}(t) dt = \sum_{j=1}^M (I_j/Q_j)B_{ij}$$

where $C_i(t)$ is the time-dependent concentration that would be measured by a detector in subcompartment $i$. The ratio $I_j/Q_j$ is determined by the distribution of injected tracer in the inlet stream, and $B_{ij}$ by intrinsic mixing within the chamber.
Cardiac Output from Isotope Dilution and Total Chamber Residue Detection

When the injected tracer is a radioisotope, the measured parameter is total chamber activity, \( R(t) \), given by

\[
R(t) = \sum_{i=1}^{N} a_i C_i(t) V_i
\]

where \( a_i \) is a counting efficiency constant for sub-compartment \( i \) (counts/sec·g), and \( V_i \) is the volume of subcompartment \( i \). Integrating both sides of Equation 9,

\[
\int_{0}^{\infty} R(t) \, dt = \int_{0}^{\infty} \sum_{i=1}^{N} a_i C_i(t) V_i \, dt = \sum_{i=1}^{N} a_i V_i \int_{0}^{\infty} C_i(t) \, dt.
\]

For flow-proportional labeling at the inlet, or perfect mixing within the chamber, it has already been demonstrated that

\[
\int_{0}^{\infty} C_i(t) \, dt = I/Q
\]

Cardiac output then is given by

\[
Q = I \sum_{i=1}^{N} a_i V_i / (\int_{0}^{\infty} R(t) \, dt).
\]

In practice, the quantity \( I \sum_{i=1}^{N} a_i V_i \) is determined by measuring total activity in the chamber at equilibrium (\( R \)) with the detector in a fixed position. It can be demonstrated that \( I \sum_{i=1}^{N} a_i V_i \) is then given by \( RV_T \), where \( V_T \) is the total blood volume within which the tracer has equilibrated.

If the measured value of the integral of the residue function, determined from Equations 10 and 6 is used in Equation 12, when tracer labeling at the inlet is not flow proportional and intrachamber mixing is imperfect, the calculated value of \( Q \) is given by

\[
Q_c = I \sum_{i=1}^{N} a_i V_i / (\sum_{i=1}^{N} a_i V_i (\sum_{j=1}^{M} (I_j/Q_j) B_{ij})).
\]

\( Q_c \) can be less than, equal to, or greater than \( Q \), and depends on the values of \( I_j/Q_j \) and \( B_{ij} \). If mixing within the chamber is perfect \( B_{ij} = Q_i/Q \), and \( Q_c = Q \).

In summary: (1) If injected tracer is well-mixed (flow proportional labeling) at the inlet to a chamber that can be characterized as a linear, constant-volume system with arbitrary but time-independent internal mixing properties, the integral of the concentration time curve at any point in that chamber is independent of location. (2) If tracer is not well-mixed (other than flow-proportional labeling) at the inlet to a chamber, the integral of the concentration-time curve at any point in that chamber depends on location, and is determined by tracer labeling at the inlet, and intrinsic mixing within the chamber, according to Equation 6. (3) Correct calculation of cardiac output from volume-of-interest activity-time curves requires either that tracer be well-mixed (flow proportional labeling) at the inlet to the volume-of-interest, or that tracer be perfectly mixed within that volume. If neither criterion is fully satisfied, calculated cardiac output can be high or low, and is given by Equation 13.

Methods

Four mongrel dogs (18–20 kg) were anesthetized with sodium pentobarbital (30 mg/kg), maintained on positive-pressure ventilation, and in each the left chest was opened and the heart exposed. A single-hole catheter with a dead space of 1.8 ml was placed into the right atrium through the jugular vein, and a one, or multiple-hole catheter, as described below, was inserted through the left atrial appendage into the left atrium. Chilled normal saline was employed as a thermal tracer, and commercial stainless-steel sheathed, ungrounded, chromel-alumel thermocouples (Omega Engineering) with an overall diameter of 0.254 mm were used as sensors for temperature measurement. Output signals were recorded on a Beckman eight-channel oscillograph recorder. The intrinsic thermocouple time constant was found experimentally to be approximately 20 msec, and the combined time constant of the thermocouple and recording galvanometer was determined to be less than 50 msec. The sensors were thus able to follow events occurring within small fractions of a cardiac cycle accurately. Electrical isolation of the sheath from the thermocouple eliminated interference from cardiac muscle depolarization. The thermocouple sheaths in turn were insulated with capillary tubing to a point approximately 1.5 mm from the tip, and the resulting localized area of exposed conductor served as an ECG electrode (V lead). The thermocouple support fixture shown in Figure 1 (left) held the thermocouple sensors in a fixed
position normal to the lumen-endocardium interface. Prior to each study, the amplifier channels of the recorder were balanced until all the thermocouples used demonstrated a voltage response that was within ±1% of the mean response to a specified temperature change.

Three thermal sensor supports were sutured to the anterior surface of the left ventricle at points that resulted in the inserted sensor tips being located at the approximate center of the inflow-outflow, middle, and apical regions [Fig. 1 (right)]. The thermocouple probes then were inserted into the supports while the sheath-tip ECG was recorded. The lumen-endocardium interface was located by observing a reversal of the ECG signal as the tip was advanced through the myocardium into the lumen. The distance between the probe tip and the endocardial surface was determined by measuring the change in dimension A-B [Fig. 1 (left)] after reversal of the probe tip ECG signal. A typical ECG signal reversal is shown in Figure 2. Each thermocouple tip was advanced 4–8 mm beyond the endocardium-lumen interface, and once the sensor locations were established they were not changed during the course of an experiment. Sensor output voltage with lead II ECG and femoral artery pressure were recorded simultaneously with temperature on separate channels of the Beckman eight-channel oscillograph recorder. Although it is difficult to assess the effective volume sensed by each probe, their small size (0.254 mm in diameter) relative to lumen dimensions should assure measurement regions which are homogeneous. Also, whereas three sensors provide limited sampling, their location in representative regions of the ventricular lumen should ensure an accurate relative measure of changes in the tracer distribution and mixing parameters studied.

Experiments were conducted by injecting chilled normal saline through the left or right atrial catheters and recording the resultant thermal transients at paper speeds of 10 mm/sec for right heart injection and 25 mm/sec for left heart injection. Four distinct left atrial catheter designs were employed, although not all in each of the four experiments; a single-hole open-end catheter, and blind-end, two, four, and twelve side-hole catheters. Each had a 2-mm inside diameter and a dead space of 0.30 ml. No attempts were made to orient the catheters within the atrium, or to synchronize the injection to the cardiac cycle. Injection was done by hand usually in less than 0.5 second. Ten to fifteen runs were made for each catheter tip configuration using approximately 3 ml of iced normal saline for left atrial injections and 10 ml of iced normal saline for right atrial injections. At the end of each procedure, the thermocouples were removed and replaced with needles at the same tip location. The heart then was excised, washed with normal saline, and within a 10- to 15-minute period, the left ventricle and atrium were injected with a solution of clear gelatin with added formalin to an approximate end-diastolic pressure of 8–10 mm Hg. The gelatin was allowed to harden (10–15 minutes), and the ventricle was sectioned, transverse to its long axis, into three segments each approximately 1.5 to 2.5 cm thick. The distance between the probe tips along the ventricular axis averaged 1.5 to 2.0 cm.

To study the effect of ventricular function on intrinsic ventricular mixing, the left anterior descending coronary artery in two of the experimental preparations was dissected free at its origin and surrounded with a removable tie so that it could be occluded temporarily. In each study, injection was made into the right atrium to ensure that tracer entering the ventricle was well-mixed (see Discussion). The coronary artery was occluded for periods up to 1 minute prior to tracer injection, and studies were done prior to and during occlusion, and after recovery.

**Data Analysis**

**Departure from Flow-Proportional Labeling at the Chamber Inlet**

The integral of the concentration-time curve at any point within the ventricular chamber has been shown to be a function of tracer distribution in the inlet stream and intrachamber mixing (Eq. 6). If intrachamber mixing does not vary during the course of an experiment, as would be expected in the normal dog ventricle, changes in the integral of the concentration-time curve at fixed points within the chamber must reflect changes in the inlet distribution of tracer. In this analysis, the departure of that integral from its average value at the three indicated thermocouple locations, as determined by a standard deviation, is used as a measure of changes in the inlet tracer distribution secondary to alterations in catheter tip design.

In each experimental run (k), the integral \( A_{ki} \) of the temperature response curve from each thermocouple (i) was calculated (using Simpson's Rule with sufficiently small step size and extrapolation where necessary) as

\[
A_{ki} = \int_{0}^{\infty} (T_{ki} - T_{ki}(t)) \, dt \tag{14}
\]

where \( T_{ki}(t) \) is the instantaneous recorded temper-
ature in subregion \( i \), and \( T_{ke} \) the equilibrium temperature prior to injection. For each run with a specific catheter tip configuration, the average value of the integral was calculated,
\[
\overline{A_k} = \left( \frac{1}{3} \right) \sum_{i=1}^{3} A_{ki}
\]
and the integral at each thermocouple location was normalized to this value using the relation
\[
A_{ki} = \frac{A_{ki}}{\overline{A_k}}.
\]
A standard deviation \((S)\) for each catheter tip and injection site was then calculated as
\[
S = \left( \frac{\sum_{i=1}^{3} \sum_{n=1}^{n} \left( 1 - \overline{A_{ki}} \right)^{2}}{3n - 1} \right)^{1/2}.
\]
An \( S \) equal to zero implies either flow-proportional labeling at the inlet to the ventricle, or perfect mixing within the ventricle. The degree to which \( S \) is greater than zero is a measure of the departure from flow-proportional labeling at the inlet (for fixed but imperfect intrachamber mixing).

**Departure from Uniform Concentration Distribution within the Chamber**

To develop a quantitative measure of concentration differences within the ventricular lumen (essential to accurate ejection fraction calculation), the average subregion temperature difference,
\[
(\Delta T)_{avg} = \left( \frac{1}{3} \right) \sum_{i=1}^{3} (T_i - T_i(t))
\]
was determined at 0.5-second intervals for several runs with right atrial injection. Time zero was taken as the time of first tracer appearance in the inflow/outflow region. The standard deviation (SD) divided by the average temperature difference was then calculated at each point
\[
SD/(\Delta T)_{avg} = \left( \frac{\sum_{i=1}^{3} ((\Delta T)_i - (\Delta T)_{avg})^2}{3 - 1} \right)^{1/2} / (\Delta T)_{avg}
\]
and plotted as a function of time.

**Results**

Typical experimental results for the normal ventricle are shown in Figures 3–6, where recorded temperature in the three indicated subregions is shown with simultaneous ECG and femoral artery pressure. Figures 3 and 4 show the response to left atrial injection with a single-hole catheter; the effects of streaming are manifest in both figures. The middle sensor in Figure 3 shows no tracer response until almost 0.3 second after a change in the inflow sensor temperature and approximately 0.2 second after the apical sensor has responded. In that run, there is evidence that most of the tracer entered the ventricle during an initial diastole, since the inflow thermocouple records an initial single sharp decrease in temperature followed by a rise. This is contrasted to the study shown in Figure 4, where it is apparent that tracer entered over at least two cycles. The inequality of areas under the temperature-time curves in these figures is also manifest. Figure 5 shows the response to left atrial injection with a four-hole catheter. Improved mixing in the left atrium is suggested by the fact that tracer is seen to enter over several cycles, as well as by the significantly smaller inequality of areas under the temperature-time curves.

Figure 6 demonstrates the response to right atrial injection. Although the areas under the three subregion curves are virtually identical, suggesting that tracer was well-mixed (flow-proportional labeling) at the mitral valve, evidence of poor intrinsic ventricular mixing is demonstrated by the relatively slow tracer washout in apical and middle regions, as well as in the phase differences in fluctuations secondary to systole and diastole. The degree of departure from a uniform spatial distribution of tracer in the ventricle is demonstrated in Figure 7 where \( SD/(\Delta T)_{avg} \) calculated from Equation 19, using the data shown in Figure 6, is plotted as a function of time. The points at which the subregion concentrations reach a maximum also are indicated.
The greatest departure from a uniform distribution occurs when tracer concentration is rising. This departure reaches a minimum just after the peak of the concentration curve, and then begins to rise, but at a slower rate. If mixing in the ventricle were perfect, no concentration differences would exist at any time. These differences approach zero at the peak of the curve because the rate of change of inlet concentration at that point is zero and, since concentration cannot change rapidly in any of the subregions, there is sufficient time for mixing to occur.

Results from the inlet streaming analysis (departure from flow-proportional labeling) using Equation 17 are summarized in Table 1. Heart rate did not vary significantly among runs with any one catheter, and where variations did occur among studies, no significant trends were noted. With left atrial injection, S is largest for the single-hole catheter, ranging from 0.19 to 0.29 with an average value of 0.25. S for the two-, four-, and twelve-hole catheters ranged from 0.09 to 0.17, with an average value of 0.14. The limited number of experiments with both two and four-hole catheters precluded a realistic separation of results from these configurations; however, results with the twelve-hole catheter probably approach the best attainable. The
The smallest value of $S$ was obtained for right atrial injection; here, the range of $S$ was between 0.03 and 0.05 with an average of 0.04. The results clearly demonstrate (1) the effectiveness of multiple side holes in enhancing tracer mixing in the left atrium, and thereby reducing inlet streaming at the mitral valve, and (2) the fact that tracer injected into the right atrium through a single-hole catheter is relatively well-mixed at the mitral valve.

Results from a typical occlusion study are shown in Figures 8 and 9. Figure 8 shows tracer response in three regions of the preocclusion (normal) ventricle, with an $S$ value of 0.04, confirming flow proportional labeling at the mitral valve. High frequency fluctuations are not in phase, but tracer appearance time in each subregion as well as the point of maximum tracer concentration (minimum temperature) does not vary by more than the equivalent of two to three heart beats (0.75 to 0.9 second). Figure 9 shows tracer response in the same ventricle following 1 minute of coronary artery occlusion. $S$ for these curves is unchanged (0.03), but tracer appearance in the apical region now occurs a full five heart beats (2 seconds) after appearance in the inflow outflow region. The times of maximum concentration differ by as much as 2.5 seconds. Decreased regularity of high frequency fluctuations in the middle region, as well as a marked diminution of these fluctuations in the apical region, also is manifest. A repeat study done 5 minutes after release of the occlusion demonstrated a return to the pattern shown in Figure 8.

Figure 10 shows a plot of $SD/(\Delta T)_{avg}$ as a function of time calculated from the data shown in Figures 8 and 9. The ventricle with compromised function

![Figure 7 Subregion temperature variation (SD/($\Delta T$)$_{avg}$, Eq. 19) following first appearance of tracer in the inflow/outflow region of the left ventricle. Points are calculated from the data presented in Figure 6.](image)

![Figure 8 Left ventricular subregion temperature response to tracer injection through a single-hole right atrial catheter in the normal ventricle prior to occlusion of the left anterior descending coronary artery. $S = 0.04$ (Eq. 17).](image)

<table>
<thead>
<tr>
<th>Dog</th>
<th>Single-hole left atrium</th>
<th>Multiple-hole left atrium</th>
<th>Heart-rate (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.29</td>
<td>0.09</td>
<td>135-150</td>
</tr>
<tr>
<td>2</td>
<td>0.26</td>
<td>0.13</td>
<td>165-180</td>
</tr>
<tr>
<td>3</td>
<td>0.24</td>
<td>0.17</td>
<td>110-130</td>
</tr>
<tr>
<td>4</td>
<td>0.19</td>
<td>0.17</td>
<td>155-165</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>0.14</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Table values represent the $S$ statistic developed in Equation 17 of the text.
shows a significantly greater disparity in regional temperature than the normal ventricle during the period of rising concentration. The difference between the normal and compromised ventricle is smallest after the peak concentration is reached. As already indicated, this is the period when the inlet tracer concentration is changing least rapidly.

Discussion

We have demonstrated that, for a single-chamber, constant-volume, constant-flow linear system with arbitrary but time-independent internal mixing properties, the integral of the intrachamber concentration-time curve at a point is independent of location if there is flow-proportional labeling of injected tracer at the system inlet. For other than flow-proportional labeling (streaming), the value of the integral depended on location in the chamber, and was a function of tracer distribution in the inlet stream and intrinsic mixing within the system. An equation for the value of the integral in terms of both parameters was presented. The development was extended further to show the effect of streaming and intrinsic non-mixing on cardiac output evaluation from the technique of radioisotope dilution and residue detection. It was shown that correct calculation of cardiac output demands either flow-proportional labeling of tracer at the inlet to the measured volume of interest, or perfect mixing of tracer within that volume. Further, a relationship was developed to show calculated cardiac output when neither criterion is satisfied.

The theoretical development assumed a constant-flow, constant-volume, linear system, and potential limitations in applying this theory to the actual time-varying system are recognized. The linearity of the overall left heart-aortic system was demonstrated by Bassingthwaighte and Ackerman (1967) in an experimental study that measured the distribution of transit times at three points in the aorta of anesthetized dogs after pulmonary artery or left atrial injection. Also, studies of the effect of time-varying flow on cardiac output calculation (Sherman, 1960; Cropp and Burton, 1966; Bassingthwaite et al., 1970) indicate that, at cardiac frequencies, effects are negligible, and it is reasonable to characterize the central circulation as a constant-flow and constant-volume system. Although the possibility of pointwise nonlinearity in the ventricle remains a potential problem, the theoretical approach used in this study nevertheless provides an insight into the effects of, and difference between, inlet streaming and intrinsic chamber nonmixing.

The following conclusions may be drawn from experimental observations made in this study: If tracer is injected into the left atrium through a single-hole, open-end catheter, streaming of tracer (other than flow-proportional labeling) into the ventricle is of major significance under virtually all conditions. Subsequent mixing of tracer within the
ventricle, as judged by means of a comparison of the regional temperature response, does occur, although a temperature equality within ±20% was rarely demonstrated before 70–80% of the tracer had passed through the system, usually in four to six heart beats. Use of blind-end, multiple side-hole catheters reduces inlet streaming by more than 50% according to the statistic developed in this study. Their use also reduces regional temperature inequalities during tracer passage. Tracer injected into the right atrium is well-mixed (flow-proportional labeling) at the inlet to the left ventricle under almost all conditions, as evidenced by the position independence of the integral of the intraventricular concentration-time curve. Even with right atrial injection and tracer well-mixed at the left ventricular inlet, there is a distinct limitation in intrinsic mixing in the normal ventricle that leads to significant regional concentration inequalities during tracer passage (although less than that evidenced with left atrial injection). These inequalities are minimal just after the intrachamber response curve peaks, and the derivative of the input function is zero. The first and most significant changes in tracer concentration following injection occur in the inflow-outflow region, with comparable changes reaching the middle and apical regions only several beats subsequently. Intrinsic non-mixing in the left ventricle is exacerbated by impaired ventricular function. The effect is most pronounced before the peak of the response curve, when the input function is changing most rapidly. Just after the peak of the response curve, when the derivative of the input function is zero (for right atrial injection), regional concentration differences in the normal and compromised ventricles appear comparable.

Significant streaming of tracer following left atrial injection and subsequent limitations in ventricular mixing are findings similar to those of Iri-sawa et al. (1960), as is the observation that tracer can be delayed significantly in reaching the ventricular apex. In contrast to their finding that tracer in the ventricle is well-mixed by the third heart beat after injection in most instances (77% of studies), we rarely found a uniform concentration distribution until most of the tracer had passed through the ventricle (usually four to six heart beats), and the difference from baseline temperature was small enough to make measurement errors significant. In any case, as Swan and Beck (1960) point out, there is no reason to expect a priori that tracer distribution should improve significantly several beats after injection, since tracer-free blood continues to enter the ventricle with each successive beat. The relative delay in the apical concentration peak following right atrial injection is a finding similar to that of Boyle (1974) who made regional conductivity measurements, although his results might be affected by flow pattern changes in the ventricle secondary to the presence of a catheter and sampling electrodes. Although it was difficult to assess the effect of heart rate on intrinsic mixing because of the limited range in the study (110–180), no consistent trend was apparent.

The Effect of Catheter Tip Configuration on Tracer Labeling at the Ventricular Inlet

We have shown that subregion measurements of the integral of the temperature-time curve can be used to characterize the relative departure from flow-proportional labeling at the inlet to a cardiac compartment. This information can be used to optimize injection and sampling locations as well as catheter design. As Table 1 clearly demonstrates, the blind-end multiple side-hole catheter significantly reduces tracer streaming at the mitral valve, probably by enhancing atrial mixing of tracer. Some difference in results between studies is expected since development of the statistic given by Equation 17 is predicated on a constancy of intrinsic mixing, and although this might occur in any single study, some variation among studies is likely. Nevertheless, the values and trends were remarkably consistent. The effects of heart rate did not appear significant within the narrow range of each study. In addition to reducing inlet streaming, the multiple side-hole catheter design resulted in smaller regional temperature variations than the single-hole open-end design.

From an experimental point of view, the effect of injection timing relative to the cardiac cycle must be considered. If the atrial injection were made at the start of the ventricular systole, there would be a finite period (the systolic ejection period) during which atrial mixing could occur. On the other hand, if the injection were made during diastole, streaming would be more significant. In these studies there was no attempt to time the injection to systole or diastole. In the large number of runs with each catheter tip design, however, the effects of timing were randomized and therefore should not bias results. It is expected that if injection were timed to the cardiac cycle, using for example an automatic R wave plus delay triggered injector, conditions for mixing with a pulse injection could be improved.

Implications for Cardiac Output Evaluation from Isotope Dilution

Cardiac output calculated from isotope dilution and residue detection is affected by streaming (lack of flow-proportional labeling) at the inlet to the measured volume of interest, as well as intrinsic mixing within that volume. Specifically, for a linear, constant-flow, constant-volume system with arbitrary but time-independent internal-mixing properties, calculated cardiac output is given by Equation 13, and can be high or low according to the values of $L/Q_j$ and $B_j$, which are functions of injection site, catheter tip design, flow, and anatomic factors (e.g., ventricular wall abnormalities). Our experimental data suggest that ventricular residue sampling for isotope injection into a proximal
atrium can lead to significant errors in the calculation of cardiac output because of imperfect mixing and non-flow proportional labeling of tracer. Indeed, in isotope studies with right atrial injection, we have found significant differences in cardiac output calculated from right and left heart regions of interest in the same patient. The former are almost always consistently high, by as much as 40-60%, whereas the latter agree closely with indocyanine green dye results (Pierson et al., 1977). The optimum procedure with right atrial injection is to sample from a left-heart region of interest, since our data indicate that passage through the right ventricle and lungs results in flow proportional tracer labeling at the left ventricular inlet.

Implications for Ejection Fraction Evaluation from Isotope Dilution

Ejection fraction from radioisotope dilution and other tracer methods is predicated on the assumption that a fractional change in measured activity during systole is equal to a fractional volume change. This is necessarily true only when tracer concentration is uniform within the ventricle. Our results demonstrate that direct left atrial injection never leads to this condition in the left ventricle. By analogy, similar problems should occur in the right ventricle with right atrial injection, and it follows that right heart ejection fraction calculated from this procedure is inaccurate. Our results do indicate that intrinsic mixing in the normal left ventricle is sufficient, if right heart injection is used, to allow for reasonable equality of regional tracer concentration just after the peak of tracer concentration, as shown in Figures 7 and 10. When tracer is injected into the right heart, the input function to the left heart is spread significantly due to passage through the lungs. As a result, the rate of rise of left ventricular tracer concentration is small in comparison to the rise following left atrial injection. In fact, at the point of peak concentration, the derivative of the input function is zero, and even though intrinsic ventricular mixing is not perfect, it is sufficient to keep regional concentration variations relatively small. Thus, left ventricular ejection fraction from right heart injection probably is accurate if the response curve prior to and after the point of peak concentration is neglected. In the compromised ventricle, errors from data prior to the peak would be even more significant (Fig. 10), although errors from the use of data taken after the peak should be comparable to those in the normal ventricle (Fig. 10). Although there is no way of knowing whether ejection fraction from data taken before or after the peak would be low or high, experimental results suggest that it might be high before the midpoint of tracer passage and slow subsequently, since impaired mixing initially delays tracer movement into the center and apical regions, and subsequently retards clearance from those regions.

References

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End-Systolic Pressure-Volume Relation
Estimated from Physiologically Loaded Cat Papillary Muscle Contractions

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SUMMARY Physiological loads were imposed on contracting isolated cat papillary muscles. The interaction of a hypothetical cylindrical ventricle with a three-element vascular impedance model dictated these physiological loads. The length-tension relation of the physiologically loaded muscle and the pressure-volume relation of the hypothetical ventricle were simultaneously analyzed while the resistive and capacitive components of the vascular impedance were varied widely. Both the end-systolic muscle length-tension relation and the end-systolic ventricular pressure-volume relation were constructed using stepwise increments in either peripheral vascular capacitance or peripheral vascular resistance. The slope of the relation line connecting the end-systolic pressure-volume points under stepwise increases in resistive load was smaller (p < 0.0005) than the slope of this line under stepwise increases in capacitive load. Therefore, the end-systolic pressure-volume relation behaves differently with respect to capacitive and resistive loads. The different loading pattern within the same beat under these varying loading conditions and the coincidence of end-systole with end-ejection in these naturally ejecting contractions are responsible for the shifts in slope of the end-systolic pressure-volume relation.

Neither the slope nor the volume intercept of the end-systolic pressure-volume relation was changed when initial muscle length was decreased from 1.0 to 0.95 lmax. When the Ca2+ concentration in the bathing solution was increased from 2.5 to 7.5 mM, the slope of the end-systolic pressure-volume relation increased (p < 0.0005), and the volume intercept of the curve decreased (p < 0.025). These results are similar to data reported for conscious animals and to data obtained from catheterization of the human left ventricle. Circ Res 46: 20-26, 1980

THE end-systolic pressure-volume relations of the intact ventricle and the end-systolic length-tension relations of isolated cardiac muscle have been the subject of considerable interest. However, conflicting experimental data have been obtained from isolated papillary muscles (Taylor, 1970), in situ papillary muscle preparations (Suga et al., 1977), isolated left ventricles (Suga and Sagawa, 1974; Weber et al., 1976) and during catheterization both in dog or in humans (Mahler et al., 1975; Grossman et al., 1977). Shortening deactivation was shown to be important in isolated muscle preparations (Taylor, 1970; Suga et al., 1977; Brutsaert and Housmans, 1977), whereas in the isolated left ventricle, end-systolic isovolumetric and isobaric contractions nearly coincide (Weber et al., 1976; Suga and Sagawa, 1974). The volume intercept (Vd) of the end-systolic pressure-volume diagram is constant and time invariant in the isolated left ventricle, whereas it changes in clinical observations (Grossman et al., 1977). Positive inotropic interventions induce parallel shifts in the end-systolic pressure-volume relation during catheterization of conscious dogs (Mahler et al., 1975; Sagawa et al., 1977). In the isolated left ventricle, a positive inotropic intervention changes the slope of the end-systolic pressure-volume relation, while the Vd remains constant (Suga et al., 1973).

In previous work (Paulus et al., 1979), an analog computer system loaded isolated papillary muscles as if they were contracting in the wall of an ejecting ventricle. This computer feedback system used a cylindrical ventricular geometry and a three-element electrical analog of the hydraulic input imped-
Inlet and intrachamber concentration distributions in tracer studies of the canine central circulation and their relation to the isotope dilution residue function.

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