Effect of Coronary Blood Flow on Radioisotope Dilution Curves Measured by Precordial Scintillation Detection

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In a comparison of radioactive bolus dilution curves obtained simultaneously by external monitoring over the precordium and by sampling from a peripheral artery, it was noted that arterial curves had a more rapid disappearance rate than precordial curves. This observation, made originally in human subjects, led to an investigation in animals designed to determine the reason for the distortion of the precordial curves. Theoretical considerations suggested that the distortion was due to the entrance of the radioactive indicator into the coronary vascular bed, thus interposing additional counts between the emptying left ventricular cavity and the detector.

Animal experiments were designed to reproduce the original observation without the interposition of extracardiac structures between the heart and the probe. In other experiments, measurements of coronary transit time were made in order to determine the mechanism by which filling of the coronary bed might distort the heart curve.

Data obtained from these experiments have been utilized in the theoretical analysis of two possible hemodynamic models relating intraventricular flow to flow in the coronary vascular bed.

Methods

Fourteen dogs weighing from 14 to 22 Kg. were anesthetized with an intramuscular injection of morphine (3 mg. per Kg.) and an intravenous injection of sodium thiopental (20 mg. per Kg.). The heart was exposed through a left thoracotomy. The pericardium was opened and the heart displaced towards the right hemithorax in order to separate it from the descending aorta. Artificial respiration was maintained through an endotracheal tube. The inferior vena cava was exposed through an abdominal incision. A 1½-inch by ¾-inch NaI crystal scintillation detector with open collimation and the crystal receded 4 cm. was placed 3 to 5 mm. above the left ventricle. Only the heart was under the proximal scope of the detector. The scintillation probe fed impulses to an events per unit time (EPUT) meter set to record the accumulated number of counts in one second of each 1.25-second interval. A catheter was placed in the femoral artery and connected to a continuous serial sampler (1.5 seconds for each sample). Thirty micros. of radioiodinated serum albumin (RISA) in a volume of 1 cc. were counted in a phantom. The isotope was then injected into the inferior vena cava or right atrium. At the moment of injection, the recording over the heart and sampling from the femoral artery were begun. Artificial respiration was temporarily suspended during the run in order to minimize intrathoracic motion. Recording over the heart was continued until a well-defined plateau was reached following recirculation. Thirty femoral arterial samples were collected in 45 seconds.

Precalibrated sampling vials were assayed in a well-type counter and weighed in an analytical balance. Specific activity ($\mu$e. per $\mu$e. of blood) of each sample was calculated and the values plotted against a time abscissa on semilog paper after correction was made for the time lag due to the 2.5 ml. volume of the catheter. The empty syringe was counted with the same geometry used prior to the injection in order to determine the exact amount injected. From the arterial dilution curves, cardiac output was calculated by the Stewart-Hamilton formula.

Cardiac output = $Q \times \frac{60}{Cdt}$ ml./min.

$Q$ = amount injected ($\mu$e.).
$C$ = specific activity ($\mu$e./ml.).
$t$ = seconds.

This value was related to the weight of the animal.
Figure 1 illustrates the sequence of heart and arterial dilution curves obtained from an open-chest dog. During the first 6 to 10 seconds, activity is recorded only over the heart in the form of a double-peaked curve as the bolus first reaches the right and subsequently the left ventricle. After the second peak is recorded over the left heart cavities, a rapid drop of radioactivity follows which describes a straight line downslope. This downslope ends in a plateau as recirculation appears in the heart after 6 to 10 seconds. Simultaneously with the beginning of the heart downslope, or even one second before, there is the first appearance of radioactive material in the femoral artery. The changes in concentration in the femoral artery describe the typical single-peaked indicator-dilution curve, i.e., rapidly increasing radioactivity reaching a peak in four to eight seconds followed by a drop until recirculation occurs. The terminal downslope of the femoral arterial curve (downstream point) is steeper than the one from the heart (upstream point). The exponential constant \( \lambda \) for both downslopes is calculated from the formula

\[
\lambda = 0.693/T_{\Delta/2}
\]

The difference between the two slopes may be expressed in the form of a ratio, thus

\[
\frac{\lambda_{\text{artery}}}{\lambda_{\text{heart}}} = \frac{T_{\Delta/2 \text{ heart}}}{T_{\Delta/2 \text{ artery}}}
\]

\( T_{\Delta/2} \) = Time required to drop activity 50 per cent.

It will subsequently be shown that this ratio is a function of coronary blood flow, and for this reason we have chosen to call the numerical value of this ratio the Coronary Flow Index (CFI = \( T_{\Delta/2 \text{ heart}}/T_{\Delta/2 \text{ artery}} \)).
In figure 2, coronary flow indices measured in 14 dogs are plotted against cardiac output per kilogram body weight. The distribution of the indices indicates that, in all but one instance, the heart disappearance rate was appreciably slower than the arterial disappearance rate. In the one exception, the two curves had identical downslopes, and the dog expired a few minutes later with ventricular fibrillation. The left coronary artery was found at autopsy to be completely occluded by a fresh thrombus at the traumatized orifice (fig. 3). There is some suggestion that very low cardiac output may be associated with larger distortion of the heart curve.

Measurements of Coronary Transit Time

Figures 4 and 5 illustrate experiments in which heart, arterial and right atrial curves were obtained after injection of the radioactive bolus into the left ventricle or coronary artery. Table 1 summarizes the data obtained from all eight experiments. When injection was made into the left ventricle (fig. 4), peak radioactivity was reached in the femoral artery at a time when it was just beginning to appear in the right atrium after traversing the coronary bed. The peak of activity in the right atrium was reached at 7.5 seconds at a time when the arterial activity had dropped to a level of 20 per cent of its maximum.

In this experiment, the coronary vascular bed retained the fraction of the bolus that went through it during a minimum of three seconds, while the left ventricle had cleared 50 per cent of the amount injected after 1.5 seconds. It must be assumed that the beginning of the filling of the coronary arteries started at some time between the injection and the appearance in the femoral artery 1.5 seconds afterwards. Since the heart rate in this experiment was 180 per minute, one-third of a second after injection, some indicator must have left the left ventricle, whereas no radioactivity was detected leaving the coronary vascular bed before three seconds. This suggests a ratio of coronary transit time to left ventricular transit time of nine in this experiment.

When the injection was made into the left coronary artery, a portion of the bolus regurgitated into the aorta and was detected in the femoral artery 1.5 seconds afterwards, as shown in figure 5. Recirculation in the femoral artery was exaggerated by the subsequent appearance of the portion of the bolus that went through the coronary bed. The appearance time in the right atrium was

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**Table 1**

Comparison of Coronary and Ventricular Transit Times

<table>
<thead>
<tr>
<th></th>
<th>Appearance time</th>
<th>Buildup time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>right atrium</td>
<td>femoral artery</td>
</tr>
<tr>
<td>Intraventricular injection</td>
<td>3  1.5  4  1.5</td>
<td>6  3  5  1.5</td>
</tr>
<tr>
<td>Left coronary artery injection</td>
<td>4.5  1.5  3  3</td>
<td>5  1.5  7  1.5</td>
</tr>
</tbody>
</table>

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Heart and arterial curves obtained in same manner described in figure 1. Left coronary artery occluded.

4.5 seconds, and the peak was reached at 7.5 seconds. It is of interest to compare the externally monitored heart curves in the two types of experiments. In the ventricular injection, the disappearance rate is considerably more rapid than that observed when the injection is made into the left coronary artery (figs. 4 and 5). The disappearance rate from the left ventricle has a T½ of 2.5 seconds, while that of the coronary artery has a T½ of 13 seconds. Ratio of coronary to ventricular transit times by this method is 5.2. McKeever,3 in a series of experiments in dogs, injected the indicator directly into a cannula feeding the left main coronary artery while sampling from the coronary sinus. His appearance times in the coronary sinus were from three to four seconds, and the T½ of disappearance was 4.6 seconds.

Theoretical Considerations

Analysis of the hemodynamic influence giving rise to the distortion of the heart curve is based on the following premises: (1) The downstream arterial disappearance curve is identical to the left ventricular disappearance curve.4 (2) The onset of ventricular emptying is followed immediately by coronary filling. (3) The bolus traverses the coronary bed at a slower rate than its passage through the ventricular cavities. (4) Since the ventricular cavities and the coronary vascular bed are both in the scope of the external detector, the observed curve is a composite of the rate of disappearance of the bolus from the cavities and its passage through the coronaries. Since the ventricular disappearance rate is given by the downstream arterial curve, the observed excess of counts in the heart curve is due to the delay of the passage of a portion of the radioactive bolus through the coronary vascular bed where each radioactive molecule has time to emanate more counts while in the scope of the detector. Considering the left ventricular cavity to be a small mixing chamber, it is desirable to analyze the characteristics of the coronary vascular bed in terms of a dynamic model that will define our observation.

Two possible dynamic characteristics for the coronary vascular bed might be considered: (a) rigid tubes, or (b) a diluting volume. If the coronary vascular bed is considered as rigid tubes issuing from a small mixing chamber, then one expects identical concentration time sequences in the two systems,
CORONARY BLOOD FLOW

since no additional mixing or dilution of the indicator occurs in the outflow tubes, and ventricular and coronary curves are identical. Employing a detector over the heart, one should record a composite consisting of the net result of adding two identical curves displaced from each other by a time interval corresponding to the transit time of the ventricular chamber. However, by adding two such curves one obtains a composite, the downslope of which is identical with the downslopes of the individual component curves (fig. 6). The observations reported in this paper do not support the tube model for the coronary circulation because the composite downslope is different from the ventricular one.

The question of whether or not coronary blood flow can be quantitated from the information derived from comparison of heart and arterial curves must be considered.

Let us analyze the possibility of measuring regional flow with the available information, if a simple tube model is assumed.

The conservation of material in the original tube and in the branches may be expressed as follows:

\[ Q = \frac{P}{Cdt} \text{ (original) (ventricle).} \]  
\[ q_1 = \frac{P_1}{C_1dt} \text{ (branch 1) (coronary vascular bed).} \]  
\[ q_2 = \frac{P_2}{C_2dt} \text{ (branch 2) (femoral artery).} \]  

Also \( Q = q_1 + q_2 \).

\[ \frac{Q}{F} = \frac{q_1}{F_1} = \frac{q_2}{F_2}. \]

From (1), (2), (3),

\[ Q/F = \int C \, dt; \]
\[ q_1/F_1 = \int C_1 \, dt; \]
\[ q_2/F_2 = \int C_2 \, dt. \]

Thus \( \int C \, dt = \int C_1 \, dt = \int C_2 \, dt. \)

In the model in which the coronary vascular bed is considered a diluting pool, one expects the concentration time history within this pool to go through the following sequence:

1. The concentration of indicator in the original chamber depends on the rate of inflow, the concentration of the entering bolus, the efficiency of detection (geometric factor), and the volume of the diluting chamber. The ratio of volume to flow in the chamber determines the transit time of the indicator.

2. With the model in which the coronary vascular bed is considered a diluting pool, one expects the concentration time history within this pool to go through the following sequence:
Figure 6

Addition of two similar curves displaced from one another by a time lag. The heavy line is the sum of the two curves.

Figure 7

Theoretical time history of concentration of radioactive bolus in the coronary vascular bed.

The quantitative relationships to be expected are best understood in terms of a simple model for the ventricular cavity and for the coronary vascular bed (fig. 9).

Let $F_1 =$ Cardiac output cc. per minute;
$C_1 =$ Concentration left cavities, mc. per cc.;
$V_1 =$ Volume left heart cc.;
$F_2 =$ Coronary blood flow cc. per minute;
$C_2 =$ Concentration in coronary vascular bed, mc. per cc.;
$V_2 =$ Volume coronary vascular bed cc.

\[ V_1 \Delta C_1 = (-F_1 C_1 + F_2 C_2) \Delta t. \quad (7) \]
\[ V_2 \Delta C_2 = (F_2 C_1 - F_2 C_2) \Delta t. \quad (8) \]
\[ \Delta C_1/\Delta t = -F_1 C_1/V_1 + F_2 C_2/V_1. \quad (9) \]
\[ \Delta C_2/\Delta t = F_2 C_1/V_2 - F_2 C_2/V_2. \quad (10) \]

Assume that
$F_2 << F_1.$

Assume that
$C_2 << C_1.$
\[ \Delta C_1/\Delta t = V_2/C_1. \quad (9) \]
\[ \Delta C_2/\Delta t = V_2/C_2 = C_1/t_2. \quad (10) \]
\[ 1/C_1(\Delta C_1/\Delta t) = -1/t_1. \quad (11) \]
This relation is best represented for this short period of observation as a straight line, when plotted on semilog paper.

\[ \Delta \log C_i / \Delta t = -1/t_1 = m_1. \] (12)

Then, \( m_1 \) is the exponential constant of the arterial downslope.

Assume same efficiency of observation for ventricle and coronary, and adding equations 9 and 10,

\[ \Delta (C_1 + C_2) / \Delta t = C_1 (-1/t_1 + 1/t_2), \]
\[ \Delta (C_1 + C_2) / C_2 \Delta t = -1/t_1 + 1/t_2. \]

Approximately,

\[ \Delta \log (C_1 + C_2) / \Delta t = -1/t_1 + 1/t_2 = m_2. \] (13)

The exponential constant of the heart downslope is \( m_2 \). If we relate the two exponential constants as a ratio,

\[ R = m_1 / m_2 = (-1/t_1)/(-1/t_1 + 1/t_2) = (t_2 / t_1) ((t_2 / t_1) - 1) = R. \] (14)

The significance of \( R \) in terms of a ratio of coronary transit time and heart cavity transit time is summarized in Table 2. From this ratio coronary blood flow is estimated in terms of per cent of normal.

Discussion

The findings reported in this paper confirm the observation first made in humans that concentration curves of radioactivity recorded over the heart following rapid intravenous injection of small boluses of \(^{131}I\) have slower disappearance rates than those obtained by sampling directly from the artery. The animal experiments show that the distortion in the precordial curves is not due to radioactivity in the chest wall, since similar distortions are observed in the absence of the chest wall when the detector is placed directly over the exposed heart.

The prolonged disappearance slope of the heart curves is due to the interposition of the bolus-filled coronary vascular bed between the emptying ventricle and the scintillation detector. A theoretical analysis based on our observations, and also those of McKeever, shows that transcoronary transit time is five to nine times longer than the transit time through the left ventricular chambers. These findings lead to the conclusion that the coronary vascular bed acts as a separate diluting pool of sufficient dimensions to cause significant distortion of the precordial downslope when compared with the arterial downslope. Where the differences in downslopes are expressed as a ratio (\( T_2 \) heart/\( T_2 \) artery), the numerical value of this ratio in excess of unity becomes a function of flow in the coronary vascular bed. A confirmatory observation was obtained in one experiment in which identical heart and arterial downslopes were obtained when the radioactive bolus was prevented from entering the left coronary artery by a thrombus at its orifice.

In the theoretical analysis, the volume of the coronary bed has an importance equal to that of flow in the determination of \( T_2 \). However, we believe that under the conditions of our experiment, in which the detector "sees" all of the coronary tissue bed, changes in the volume would have little or no effect on cor-
Figure 9
Schematic representation of hemodynamic model in which coronary vascular bed is considered a diluting chamber ($C_2 < C_1$).

Coronary flow index. The rate of emptying of the bolus would depend on the coronary volume, as well as on the flow rate. Since the emptying of the coronary bed is not observed under the conditions of our experiment, the volume has little or no effect on the coronary flow index.

Another parameter that influences the estimated value of $F_2$ (table 2) is the ventricular cavity transit time ($t_1$). If two individuals have a common coronary flow index of 1.5, and one has a cardiac output of 5 L./min., while the other one of 10 L./min. the individual with larger cardiac output will have a shorter $t_1$. In order to keep the ratio of three, $t_2$ must also be shorter by the same factor. This, in turn, implies that $F_2$ will be larger. Thus, coronary flow index will remain constant if coronary flow increases in proportion to the cardiac output, and if ventricular transit time varies inversely with the cardiac output.

It is further implied that increase in the residual ventricular volume may lengthen $T_1$ in the presence of an unchanged cardiac output, diminishing the significance of the coronary flow index in the presence of a failing heart.

Intracardiac shunting would invalidate coronary flow index by introducing an additional recirculation distortion into the down-slope of the curves.

Summary
Two series of animal experiments are reported. In the first of these, the disappearance rates of intravenously injected radioactive boluses were monitored over the heart and from a peripheral artery. The disappearance rate over the heart was shown to be slower than in the artery. In a second series of experiments in which injection was made into the left ventricle or into a coronary artery while sampling from the right side of the heart, it was shown that the coronary transit time was several times longer than the left ventricular transit time. The prolonged presence of the radioactivity in the coronary vascular bed accounts for the difference in the heart and arterial disappearance slopes. A ratio of these two slopes may provide an index of coronary blood flow.

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