Measurement of Myocardial Blood Flow
Indicator-Dilution Technique

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A "CLOSED" method for the accurate measurement of myocardial blood flow is still to be achieved. In 1956, Henly et al. described an indicator-dilution technique for assessing myocardial blood flow. This approach led us to construct a suitable model for simulating a systemic-coronary circuit. Observations with this system suggested that an indicator-dilution technique might be applicable to measuring myocardial blood flow in the intact animal, and the method was, therefore, adapted to the dog. This paper details our experiences with the model system and the intact animal.

Theory

The indicator-dilution technique for measuring cardiac output was originally described by Stewart in 1897, but did not attain general acceptance until the work of Kinsman, Moore, and Hamilton in 1929. Nylin and Celander, and MacIntyre have since introduced the use of radioactive isotopes as the indicator.

In the application of this method to the calculation of myocardial flow, it is critical that the time lag between the appearance of activity from the coronary circuit and that of the most rapid noncoronary circuit be sufficient for the "time-concentration" curve obtained from the myocardial flow to be well on the downslope before the activity from the next most rapid circuit enters the sampling site. If this is so, the dilution curve plotted on semilogarithmic paper would have the appearance shown in figure 1.

Given such a curve, the coronary flow may easily be calculated. The fraction of originally injected indicator entering the coronary arteries is equal to the ratio of coronary flow to cardiac output:

\[ \frac{Q_c}{Q} = \frac{Q_c}{Q_{co}} , \]

where \( Q_c \) = quantity of tracer entering coronary arteries, \( Q \) = amount of originally injected tracer, \( Q_{co} \) = coronary flow, and \( Q_{co} \) = cardiac output. This quantity of indicator \( Q \) in turn is also equal to:

\[ \int_0^{Q_{co}} C_c Q_{co} dt = Q , \]

where \( C_c \) = concentration of indicator obtained from coronary curve.

Therefore, if \( Q_{co} \) is assumed to be constant, these two equations can be rearranged as follows:

\[ Q_c = \frac{(Q_{co})^2}{Q} \int_0^{Q_{co}} C_c dt , \]

which is the equation used to compute myocardial blood flow from the dilution curves obtained.

Model Studies

A diagrammatic sketch of the model used to simulate the systemic-coronary circuit is shown in figure 2. Fluid (tap water) is pumped by a Sigmanotor pump to a double funnel, which permits a constant head of pressure of any desired magnitude to be maintained throughout the system. Flow rates may be adjusted by manipulating the arrangement of the funnels and by choosing tubing of appropriate diameter.

Three separate circuits are then led off from the double-funnel pressure source. Circuit (1) represents the "fast," or myocardial, vessels. Circuits (2) and (3) represent the systemic circulation. Two circuits of different length were chosen in order to simulate more closely the condition obtained in the intact animal—e.g., circuit
Figure 1

Theoretical indicator-dilution curve for myocardial blood flow which would be expected if the coronary circuit were significant shorter than the shortest systemic circuit.

(2) could represent the cerebral portion of the circulatory system, while circuit (3) could represent the trunk and lower extremities.

All three circuits were then brought together to form one circuit, representing the venous return to the right side of the heart. Into each circuit was incorporated a Manostat predictability flowmeter (FM), to serve as a check on the flow rates calculated from the dilution curves.

A known amount of indicator was then injected into the system. The indicator-dilution curve from circuit (1) was obtained by monitoring the concentration of indicator traversing the circuit in a scintillation counter (SC) of the well type and recording this activity continuously on an Esterline-Angus recorder by means of a Berkeley count rate computer. From this record, an indicator-dilution curve could be obtained and the flow rate computed. When properly integrated, the curve gave the total flow in ml/min. The values obtained from the dilution curve were checked against total flow (= cardiac output) as measured by the flowmeters.

Samples were removed every two seconds from a site distal to the confluence of all three circuits. These samples were then counted in a standard well counter and the time-concentration curve for each experiment drawn. A typical curve obtained from the model is shown in figure 3. From these curves and the principles discussed before, the flow through the "fast" circuit (coronary flow) could be calculated. These results were then checked against actual flowmeter readings.

Results

Results obtained from the model system are shown in table 1. In column (A) are listed the values for total output of the system as actually measured by the flowmeters. These are assumed to represent the actual flow rates. In column (B) are the total outputs as calculated from the indicator-dilution curve obtained on the Esterline-Angus recorder from the "fast" or "coronary" circuit. Column (C), then, expresses the differences between the calculated and measured outputs as a percentage of the latter. The average deviation in four trials is 2.6 per cent.

The concentration of indicator traversing the "fast" circuit was then determined and expressed as a percentage of the total concentration of tracer passing through the entire system. It was assumed that the flow rates through the "fast" circuit would be the same percentage of the total flow rate. These percentages are tabulated in column (D). In column (E), the flow rates in the "fast" circuit calculated from the measured total flow rates (column A) are listed. For comparison, the flow rates in the "fast" circuit actually measured by flowmeter are listed in column (F). The differences between the actually measured and the calculated flow rates are expressed as a percentage of the former in column (G). The average per cent deviation in four trials was zero.

As a check on the validity of the calculated flow rates, the flow through the "fast" circuit was then calculated using the total flow rates as calculated from the indicator-dilution curve (column B) and the percentage of total indicator traversing the "fast" circuit (column D). These values appear in column (H) of the table. The differences between these values and the actually measured flow rates through the "fast" circuit (column F) are expressed as a percentage of the latter and appear in column (J). As may be seen from the table, the average per cent deviation was -2.6 per cent.

Animal Studies

Methods

A no. 8 Gournard catheter was placed in the right or left main pulmonary artery via a jugular vein under fluoroscopic guidance. A no. 280 polyethylene catheter, 20 feet long, opacified by 70 per cent Crokon was similarly placed 3 to 4

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MYOCARDIAL BLOOD FLOW

Injection Site

WATER

Sampling Site

Figure 2

Diagrammatic sketch of the model system. (FM) means flowmeter, (SC) means scintillation counter, (1) represents the "coronary circuit," and (2) and (3) represent the "systemic circuits."

em. proximal to the Courmand catheter via the opposite jugular vein. The animals were then given heparin, 3 mg./Kg.; in addition, all catheters were siliconized to minimize clotting. In those animals in which the superior vena cava was sampled, a second no. 280 polyethylene catheter was placed with its tip just proximal to the entrance of the azygos vein into the superior vena cava.

For determination of simultaneous cardiac output, another no. 280 polyethylene catheter was inserted into a femoral artery proximally, led through a specially drilled scintillation counter, and inserted distally into the same femoral artery.

Figure 3

Due-dilution curve based on actual data developed from the model.

This permitted a continuous flow of blood past the scintillation counter. Activity of the blood was fed into a Berkeley sealer, then into a Berkeley count rate computer, and recorded on an Esterline-Angus recorder. In this fashion, a continuous record of the time-activity of indicator in the femoral artery was obtained.

Another no. 280 polyethylene catheter was inserted into a femoral vein for convenient drawing of the 10-minute blood sample for calculating the animals' blood volume.

The polyethylene catheter in the pulmonary artery was connected to a variable source of negative pressure which could be turned on or off as desired. The tubing was then filled with blood so as to have the same viscosity along the entire length of the catheter. Then, the negative pressure was adjusted so as to give the maximum rate of

Table 1

Results Obtained in the Model System Showing the Differences in Flow Rates Between the "Fast" and "Slow" Circuits*

<table>
<thead>
<tr>
<th>Determination</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>943</td>
<td>907</td>
<td>+ 5.7</td>
<td>50.8</td>
<td>479</td>
<td>490</td>
<td>- 2.2</td>
<td>506</td>
<td>+ 3.3</td>
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<td>II</td>
<td>770</td>
<td>764</td>
<td>- 0.8</td>
<td>37.8</td>
<td>291</td>
<td>309</td>
<td>- 5.8</td>
<td>289</td>
<td>- 6.5</td>
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<tr>
<td>III</td>
<td>696</td>
<td>674</td>
<td>- 0.3</td>
<td>79.5</td>
<td>534</td>
<td>504</td>
<td>- 9.9</td>
<td>552</td>
<td>- 9.5</td>
</tr>
<tr>
<td>IV</td>
<td>775</td>
<td>819</td>
<td>+ 5.7</td>
<td>39.3</td>
<td>309</td>
<td>310</td>
<td>- 1.9</td>
<td>322</td>
<td>+ 3.9</td>
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<tr>
<td>Average</td>
<td>+ 2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 2.6</td>
</tr>
</tbody>
</table>

*(A)—total flow measured by flowmeter (ml./min.); (B)—total flow by calculation (ml./min.), \( \dot{Q} = \mathcal{A} \dot{Q} \) where \( \dot{Q} = \text{flow}, \mathcal{A} = \text{amount of indicator injected}, \mathcal{A} = \text{area under curve}; (C)—per cent error, A-B/A \times 100; (D)—"fast" circuit percentage of total concentration; (E)—"fast" circuit flow calculated from total flow as measured by flowmeter, A \times D (ml./min.); (F)—"fast" circuit flow measured by flowmeter (ml./min.); (G)—per cent error, F-E/F \times 100; (H)—"fast" circuit flow calculated from columns (B) and (D), B \times D; (J)—per cent error, F-H/F \times 100.
Table 2
Effects of Lamination in the Catheters

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Expected</th>
<th>Actual</th>
<th>Time</th>
<th>Amount withdrawn</th>
<th>Catheter size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>143</td>
<td>179</td>
<td>30</td>
<td>13.2</td>
<td>280</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>135</td>
<td>30</td>
<td>15.8</td>
<td>280</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>138</td>
<td>45</td>
<td>21.1</td>
<td>330</td>
</tr>
<tr>
<td>4</td>
<td>186</td>
<td>198</td>
<td>30</td>
<td>17.1</td>
<td>280</td>
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<tr>
<td>5</td>
<td>126</td>
<td>195</td>
<td>45</td>
<td>11.6</td>
<td>280</td>
</tr>
</tbody>
</table>

*Expected—the maximum length of catheter calculated to contain radioactive blood, in inches. This was derived from the amount of blood withdrawn and a knowledge of the volume of the catheter per unit length. Actual—the actual length of the column of radioactive blood contained in the catheter, in inches. Time—time of withdrawal through the catheter, in seconds. Amount withdrawn—the actual measured amount of blood withdrawn into the catheter, in ml. Catheter size refers to polyethylene tubing sizes.

Blood flow possible. The system was connected by a three-way stopcock to a photographic time recorder, in such a fashion that the time of withdrawal was accurately determined from the lines made when the negative pressure source was turned on and off. Time of withdrawal was usually 30 seconds.

A known amount of radioactive iodinated human serum albumin (Rise) was then injected into the pulmonary artery via the Cournand catheter. Both catheter and syringe had been previously calibrated to deliver a known volume of fluid. Time of injection was under 0.2 second. As soon as injection of Rise was completed, withdrawal of blood through the no. 280 polyethylene catheter in the pulmonary artery was begun and continued for a predetermined length of time. At the end of the chosen time interval, the catheter was clamped and removed from the animal. Both ends were immediately stoppered with appropriately designed plugs. The catheter was then placed in a bath of dry ice and alcohol which immediately froze the blood in the tubing and prevented sedimentation and segmentation of the column. When a catheter had been placed in the superior vena cava, it was treated in the same way.

The blood displaced from the catheter was collected in a previously weighed flask; by measuring the weight of this flask after blood withdrawal was completed, calculation of the amount of blood withdrawn could be made. The volume of the catheter per unit length had been previously determined. From this and the amount of blood withdrawn, it was a simple matter to calculate the maximum length of the column of radioactive blood in the catheter. This served as a check on the accuracy of the method, and gave a measure of the degree of lamination occurring along the tube.

Ten minutes after injection, a sample of blood was withdrawn from the femoral vein for a blood-volume determination and the simultaneous activity of blood passing the scintillation counter through the femoral arterial catheter was noted on the Esterline-Angus record. As soon as this had been done, the femoral arterial catheter was removed and the pulmonary artery catheter monitored. This was accomplished by counting segments of catheter equal to the diameter of the scintillation crystal. Counts were recorded for one minute. The catheter was monitored until several successive segments gave results which coincided with the previously determined background count. The superior vena cava catheter was treated in a similar manner in those experiments in which caval blood was withdrawn.

Results and Discussion

Studies from 14 animals are available for review. Eleven had samples taken only from the pulmonary artery, while three additional animals were simultaneously sampled from the superior vena cava and pulmonary artery.

Curves were plotted and analyzed, as discussed under Animal Studies, Methods, and Theory.

Figure 4 is representative of those curves obtained from animals which underwent pulmonary artery sampling only. As may be noted, the curve is monotonic, i.e., it continues to rise well past the time one would rea-
Table 3
Decrease in Lamination After Changing from Negative Pressure to Gravity Drainage

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Expected</th>
<th>Actual</th>
<th>Time</th>
<th>Amount withdrawn</th>
<th>Catheter size</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>78</td>
<td>84</td>
<td>30</td>
<td>7.2</td>
<td>280</td>
</tr>
<tr>
<td>7</td>
<td>94.5</td>
<td>97.5</td>
<td>30</td>
<td>8.8</td>
<td>280</td>
</tr>
<tr>
<td>8s</td>
<td>78</td>
<td>81</td>
<td>30</td>
<td>7.2</td>
<td>280</td>
</tr>
<tr>
<td>8p</td>
<td>117</td>
<td>120</td>
<td>30</td>
<td>10.6</td>
<td>280</td>
</tr>
<tr>
<td>9s</td>
<td>87</td>
<td>72</td>
<td>30</td>
<td>7.9</td>
<td>280</td>
</tr>
<tr>
<td>9p</td>
<td>120</td>
<td>122</td>
<td>30</td>
<td>11.0</td>
<td>280</td>
</tr>
</tbody>
</table>

*s = superior vena cava; p = pulmonary artery.

sonably expect caval return of radioactive blood to be entering the right heart. All curves obtained from the pulmonary artery sampling site were of this same form. Numerous plots were made using a variety of coordinate combinations, but at no time was it possible definitely to separate the component circuits making up the blood flow through the pulmonary artery.

In view of the divergent results obtained from the model system and the animals, the time relationships existing between the coronary circulation and the fastest noncoronary circuit entering the right heart were determined by sampling simultaneously from the pulmonary artery and superior vena cava. Three experiments in which this approach was used constitute group III and are illustrated by figure 5. The solid line represents the time-concentration curve obtained from the pulmonary artery, and the broken line that obtained from the superior vena cava. The activity in the two circuits appears practically simultaneously. In none of the three experiments was there a sufficient time difference between the appearance of radioactivity in the two catheters to permit a true separation of time-concentration curves.

As may be seen in figure 5, the activity in the two circuits is not equal. If a simultaneous curve obtained from the inferior vena cava were plotted on the same graph, it would appear, at first glance, that simple subtraction of the sum of activities in the two cavae from that in the pulmonary artery would give the activity due to the myocardial circulation. However, this is impossible unless the flow through each cava is known. This is necessary for determination of the actual amount of indicator present in each circuit. Furthermore, if the flow through both cavae were known, simple subtraction from the cardiac output would yield the myocardial blood flow.

From the foregoing, it would appear that the curves obtained from the pulmonary artery are composite and that separation of the components cannot be achieved by this method. It would seem, in the dog at least, that the circulation times through the coronary circuit and the most rapid noncoronary circuit emptying into the right side of the heart do not differ sufficiently to make it possible to assess myocardial blood flow by this technique.

An analysis of the data from the model (fig. 3) shows that the length of the first diphasic curve far exceeds that which would be expected if this circuit truly represented coronary flow as it occurs in the intact organism. This curve, therefore, is artificial, and although it demonstrates the feasibility of distinguishing between a number of circuits emptying into a common site, it does not, in fact, correspond to the situation as it exists in vivo.

Another important limitation of this technique is the lamination of the blood in the catheters. Table 2 shows the effect of this factor. The values under the column headed...
"expected" represent the maximum length of the column of radioactive blood as calculated from the amount of blood removed. The column headed "actual" represents the actual length of the column of radioactive blood as determined by monitoring the catheter in the scintillation counter. It is apparent that the Risa extended farther along the tube than could be reasonably expected and, therefore, lamination may have been occurring. Increasing the size of the catheter did not appreciably alter this factor. Gravity drainage was then substituted for negative pressure, and table 3 shows the improvement obtained. However, the effect was not entirely eliminated. In those experiments in which the superior vena cava and pulmonary artery were sampled simultaneously, the effect was practically equal, and it is doubtful if it could be invoked as a factor in the results obtained.

Summary

Our experiences with an indicator-dilution technique for measuring myocardial blood flow have been detailed. It is concluded that this approach is impractical, in the dog at least, due to the lack of separation between the circulation times of the coronary and the most rapid noncoronary circuits. This precluded the possibility of obtaining accurate definition of the various components making up the composite curve obtained. A different approach to the solution of the problem of measuring coronary blood flow must be adopted.

Acknowledgment

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References

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