The Determination of Cardiac Output by a Continuous Recording System Utilizing Iodinated (I\textsuperscript{131}) Human Serum Albumin

I. Animal Studies

By William J. MacIntyre, Ph.D., Walter H. Pritchard, M.D., Richard W. Eckstein, M.D., and Hymer L. Friedell, M.D.

A method is outlined for the determination of cardiac output by the injection of iodinated (I\textsuperscript{131}) human serum albumin and continuous recording of the dilution curve. The calibration of the flow system by means of the final dilution and blood volume is discussed along with the possible application to an external measuring method. The results of eight dilution curves obtained from dogs are presented and the calculated cardiac outputs compared with the values measured by the rotameter method.

Estimation of cardiac output by the injection method has been described by Kinsman, Moore, and Hamilton,\textsuperscript{1} using dye, and by Nylin and Celander,\textsuperscript{2} utilizing radiophosphorus-tagged red cells. In this method the dilution of the injected substance as a function of time is determined. Since the resultant dilution curve is necessarily dependent upon the volume of flow, the cardiac output in terms of liters of flow per unit time may be estimated.

In both these methods the dilution is determined by serially sampling arterial blood at short time intervals. In the first method the dilution may be determined colorimetrically and in the second method by beta particle assay methods. With the successful use of iodinated (I\textsuperscript{131}) human serum albumin in determinations of blood volumes\textsuperscript{3, 4} the possibility of a continuous recording of the dilution curve utilizing gamma ray assay methods seemed feasible. There would be several advantages to such a method: (1) the serum could be used directly with no incubation required; (2) the absorption of gamma rays in small thicknesses of tissue is negligible so that a direct reading of the activity in the blood can be made during the time it is flowing; and (3) accurate timing of the dilution curve is more easily obtainable.

Method

Approximately 100 \( \mu \text{c.} \) of iodinated (I\textsuperscript{131}) human serum albumin were injected in the jugular vein of open chest, heparinized dogs weighing 10 to 25 Kg. The right femoral artery was cannulated into a rubber tube of about 3 mm. diameter, and this rubber tubing fixed over a gamma detector of high sensitivity. Blood was allowed to flow through the tube into an open beaker, with the rate of flow adjusted by a screw clamp to approximately 30 cc. per minute, or was re-led into the distal portion of the proximally cannulated femoral artery. The inscribed curves and calculated outputs were essentially unchanged by this procedure. The dilution curve was obtained by plotting the radioactivity of the blood flowing over the detector as a function of time. This curve was recorded automatically by an Esterline-Angus Graphic Meter, but as the counting rate responded logarithmically, the curve was redrawn to a linear scale for an accurate representation of the dilution. The absolute activity was then determined by calibrating the flow system with a known concentration of I\textsuperscript{131} solution. The calibration method chosen for the following work involved the determination of the final dilution (blood volume) by withdrawing an arterial sample of whole blood 10 minutes after the iodinated (I\textsuperscript{131}) human serum albumin was injected. The specific activity of the whole blood was measured in vitro in terms of \( \mu \text{c.} \) per cc. and the flow system calibrated by ob-
servation of the response of the system in vivo to this known activity at final dilution. This is then the response of the gamma detector to a known concentration of activity in terms of counts per minute per μc. per cc. A schematic diagram of the experimental setup is shown in figure 1.

**Equipment**

With application of this method to humans, specific activities as low as 0.02 to 0.03 μc. per cc. were anticipated. As the volume sampled in the flow stream is about 0.7 cc. the total activity present would be too low for successful gamma assay by a Geiger counter. For this reason a scintillation counter of a type previously described was used. This counter exhibited a sensitivity to gamma radiation of I\textsuperscript{137} of about fifty times the sensitivity of a conventional brass-wall Geiger counter.

For recording the activity passing through the rubber tubing as a function of time the conventional counting rate meter is not satisfactory because of the memory effect, in which the count at any time is influenced by the previous count recorded.\textsuperscript{6} This can be compensated for by allowing sufficient time for the rate meter to reach equilibrium, but such time is far in excess of the time of the normal dilution curve. To overcome this difficulty a Berkeley Counting Rate Computer Model 1600 was used in conjunction with a scaler and Esterline-Angus Graphic Meter. The computer is activated by the resultant pulse from a scaler after the collection of a predetermined number of counts. As each reading is a measurement of the time to collect this predetermined number of counts, each reading is completely independent of any previous reading.\textsuperscript{*} The chart speed of the Esterline-Angus Graphic Meter was set at 12 inches per minute. From this base line the response of the concentration was fixed in time with sufficient data readings taken during the 20 to 40 seconds of the primary circulation to determine the dilution curve.

**Calculation of Cardiac Output**

The general shape of the dilution curve and the equation describing the primary circulation have been fully discussed in previous works,\textsuperscript{1, 2} and are illustrated in figure 2. Both methods utilize an extrapolation of the descending curve before recirculation begins, as shown by the dotted line of figure 2, and both derive an expression relating the injected activity to the concentration and flow during the time of the primary circulation. The quantity of injected material, I, may then be expressed as the product of the concentration, c, and the rate of flow, F, integrated over the entire time:

$$I = \int_0^\infty cF \, dt$$

Provided the rate of flow, F, is considered to be constant, the following expression may be used for its solution:

$$F = \frac{I}{\int_0^\infty c \, dt}$$

\textsuperscript{*} A complete description of the counting rate computer is given in the manual of operation for this instrument. Berkeley Scientific Company, Richmond, Calif.
where \( B = \int_{0}^{\infty} c e^{-\lambda t} dt = \frac{c_0}{\lambda} \)

where \( c_0 \) is the value of the concentration at point \( B \) and \( \lambda \) is the constant determined by plotting the logarithm of the concentration along the line \( BC \) of figure 2 against time.

This reduces the expression to:

\[ F = \frac{I}{A + B} \]

The concentration, \( c \), was determined as outlined previously by comparison of the known activity of the final arterial blood dilution at 10 minutes as measured in vitro with the response of the detector to the same dilution at the final part of the curve at the same time. This is shown as point \( F \) on figure 2. Since the injected dose, \( I \), is equal to the product of the circulating blood volume, \( V \), and the specific activity of the final dilution, \( c_f \), we may write:

\[ F = \frac{c_f}{A + B} V \]

Since the first term on the right is a ratio, it is seen that the specific activity at final dilution, \( c_f \), may be expressed in terms of counts per minute at point \( F \) and the dilution curve expressed with an ordinate of counts per minute. This is important in the application to any external counting method since the final value of the dilution curve may calibrate the flow system when other means would be extremely difficult.

To look at this descriptively, the above expression may be rewritten with a substitution of the product of the average concentration, \( c_{av} \), and the time, \( T \), of the dilution for the area, \( A + B \). Now as the final dilution, \( c_f \), shows the concentrations obtained when diluted by the total blood volume, the ratio \( \frac{c_f}{c_{av}} \) shows what fraction of the blood volume must have been ejected by the heart during time \( T \). Output per unit time is then obtained by dividing by \( T \):

\[ F = \frac{c_f V}{c_{av} T} \]

This is similar to the equation used by Kinsman, Moore, and Hamilton.\(^1\)

**RESULTS**

Simultaneously with these determinations the cardiac output was determined by an optically recording rotameter\(^*\) inserted into

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Dilution Method cc./min.</th>
<th>Rotameter Method cc./min. (as measured)</th>
<th>% Deviation</th>
<th>Rotameter Method cc./min. (with 3% added for coronary flow)</th>
<th>% Deviation</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1870</td>
<td>1385*</td>
<td>21*</td>
<td>1454*</td>
<td>15*</td>
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<td>1220</td>
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<td>10</td>
<td>1160</td>
<td>5</td>
</tr>
<tr>
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<td>1245</td>
<td>1110</td>
<td>12</td>
<td>1165</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>1960</td>
<td>1750</td>
<td>12</td>
<td>1838</td>
<td>7</td>
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<tr>
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<tr>
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<td>15</td>
<td>877</td>
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<tr>
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<td>1930</td>
<td>1748</td>
<td>10</td>
<td>1835</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>2210</td>
<td>1874</td>
<td>18</td>
<td>1968</td>
<td>12</td>
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Average deviation = +15 +9

\(^*\) The major vessels in the upper thorax were ligated and the head was supplied through the left common carotid only.

The thoracic aorta just distal to the arch.\(^7\) The vessels arising from the aortic arch proximal to the rotameter were ligated and cannulas inserted into their distal ends. Flow to these areas was incorporated into the total metered flow (cardiac output) by connections to the outflow side. By this technic total cardiac output except for coronary flow was measured. The results of both methods are shown in table 1, and typical dilution curves by figures 3 to 6.

The dilution method averaged values about 15 per cent higher than the recorded corresponding values obtained on the rotameter, with a variation between 10 per cent higher

\(^*\) Expenses for the rotameter experiments were defrayed by a grant to Dr. Richard W. Eckstein from the Cleveland Heart Society.
and 21 per cent higher. Part of this deviation is due to the fact that the rotameter did not measure the coronary flow and, in experiment 1, probably a small portion of the head flow.

Although the coronary flow is usually taken as 5 per cent of the cardiac output, Eckenhoff, Hafkenschiel, and Landmesser have pointed out that this proportion can be much higher (perhaps to 10 per cent or more) when the circulation is depressed. Even assuming only a 5 per cent addition for coronary flow the agreement is still within 9 per cent, which is within the 11 per cent estimate for the dilution method by Werkö and co-workers. Since

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<tbody>
<tr>
<td>3</td>
<td>cc./min. 1245</td>
<td>cc./min. 1110</td>
<td>3a</td>
<td>cc./min. 791</td>
<td>cc./min. 1850</td>
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<tr>
<td>4</td>
<td>1960</td>
<td>1750</td>
<td>4a</td>
<td>1210</td>
<td>1620</td>
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the error is always on the high side, however, it is possible there is a small systematic error in the method.

In the procedure used, no phase was critical except that of insuring a sufficiently rapid flow of blood through the rubber tubing. When this flow was constricted sufficiently (approximately 5 cc. per minute), a slow dilution curve (and consequently a low output) was obtained. This was considered to be due to a stagnation of the blood in the tubing, resulting in a broader dilution curve which was falsely recorded as a slow circulation in the animal. This effect was checked by taking two successive runs on each of two dogs, one with slow tube flow and one with fast tube flow, and comparing the results with the rotameter outputs.

As seen in table 2 the fast flow gives a close correlation with the rotameter values while the slow flow does not. Provided the flow is fast enough to prevent pooling in the tube, the rate of tube flow should have no effect on the output.

Since no other difficulties were encountered and since the over-all correlation appeared satisfactory, further work is anticipated applying this method to man. In this case, correlation will be obtained by means of the Fick method.

**Summary**

Iodinated (I\(^{131}\)) human serum albumin has been injected into the jugular vein of dogs and a continuous record of the dilution obtained as a function of time. The cardiac output from these curves has been calculated from the derived formula and compared with values obtained from the rotameter method run simultaneously. The comparison of these two methods has been found to agree within 9 per cent.

**Acknowledgment**

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**References**


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