Radioactive Isotope Determination of Myocardial Blood Flow by Surface Counting and Ratio Formula

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Estimation of cardiac output by the indicator-dilution method has been described by Kinsman, Moore, and Hamilton\(^1\) utilizing dye; however, radioactive methods for determination of cardiac output owe their inception to Prinzmetal and co-workers,\(^2\) who recorded radioactivity as a function of time by means of a counter over the heart after an intravenous injection of radioactive Na\(^{24}\). Nylin and Celander\(^3\) utilized red cells tagged with radioactive phosphorus. They determined the dilution by serially sampling arterial blood at short time intervals and using beta-particle assay methods; an external counter was not adaptable to this method.

Huff and associates\(^4\) used a narrow-angle scintillation counter and radioactive iodinated human albumin and found an excellent correlation of radioactive determinations of cardiac output with those obtained by cardiac catheterization. By this method, the passage of radioactive substance through the heart is detected by placing a gamma-ray detector on the skin between the first and second ribs at the left parasternal line. Count rates as a function of time are obtained that are similar to those obtained by direct arterial blood sampling. The curve written during the initial passage of the radioactive substance through the heart presents two peaks that represent the tracer passage through the right and left ventricles, respectively. The area under the extrapolated curve is divided into the equilibrium counting rate. The dimension of the cardiac output thus obtained is in terms of a multiple or fraction of the subject’s blood volume per unit of time. Conversion to liters per minute is made by determining the blood volume of the isotope-dilution technic. As indicated by MacIntyre et al.,\(^5\) there are several advantages to this method: (1) the serum can be used directly without incubation, (2) the absorption of gamma rays in small thicknesses 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 easily obtainable.

Sevelius and Johnson,\(^6\) in utilizing this method for the determination of cardiac output, described a third peak, which closely followed in time the two peaks of the heart curve. They suggested that this third peak coincided with the appearance of radioactivity in the periphery and was possibly related to myocardial blood flow.

The present clinical study was designed to evaluate critically the reliability of the described method for the determination of myocardial blood flow. A total of 47 subjects was involved in this study and the results are included with the previous Wichita study of 14 subjects in 1960 to 1961, which was handled in a similar manner.\(^7\) Twenty-four of the subjects were women and 37 were men.

Materials and Methods

Equipment

The tracings were obtained on a two-channel direct-writing recorder. Each channel was connected to a scintillation detector and a rate meter. The scintillation detectors had a 1½ by 2 inch sodium iodide crystal, shielded by 1/8-inch lead, enclosed in a cylindrical collimator. The crystal was located flush with the collimator window. One scintillator probe was positioned over the heart to obtain the cardiac output curve. The second scintillation counter was positioned over the femoral artery for timing the appearance of the isotope. A lead cylinder with a wall 2 inches thick was

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used for further collimation of the scintillation counter used to obtain the cardiac output curve. The output of the precordial scintillation detector was fed into a linear rate meter with an integrating condenser, which allowed the rate meter to go full scale in 0.5 second. Full scale represented 25,000 c.p.m. on the heart channel and 10,000 c.p.m. on the femoral channel. The rate meter was connected to a rectilinear recorder (Texas Instruments, Inc.) recording at a speed of 12 inches per minute. A siliconeized tuberculin syringe was used for injection of the tracer dose. The tracer substance was radioactive iodinated human albumin (RISA). The volume of the dose was 0.2 to 0.4 ml. The amount of radioactivity was about 40 μc. It is optimum to have the peaks of the heart curve reach a height of about 20,000 counts per minute. The extrapolation of the heart curve and myocardial blood flow peak was made mathematically by a French curve of best fit. The areas under each curve were determined with a planimeter. The projection of the heart on the chest wall was determined clinically. Procedure The subject was placed on a bed, and the blood volume was determined by the radioactive tracer-dilution method before the cardiac flow rate tracings were recorded.

One lead-collimated probe was positioned over the third left intercostal space 2 cm. left of the midclavicular line and the other was placed over the femoral artery. The purpose of the femoral artery record was to register the start of the peripheral circulation of tracer in order to detect the presence of a third peak on the heart curve. After the equipment was calibrated, the radioactive serum albumin was injected as rapidly as possible into the median basilic vein of the left arm. Almost immediately, the precordial count radioactivity increased, reached a peak in 2 seconds or less, and fell away as the bolus of isotope moved from the heart into the lesser circulation. A second peak appeared as the bolus returned to the left ventricle. When the radioactive bolus traversed the greater circulation and returned to the heart, it introduced a background count that was related in amount to the blood volume.

Ink tracings produced in the 30 to 45 seconds of the test provide a time history of the passage of the radioactive bolus through the circulatory system, from which flow rates may be estimated. However, the data on the precordial probe recording are clouded by other smaller duration excursions which are produced by normal background radiation. The extrapolated curves, the subject's physical characteristics and identification, and the blood volume are the data upon which the calculations of the cardiac output and myocardial flow were based.

Calculation of Cardiac Output and Myocardial Flow

Two mathematical problems are posed in the reduction analysis, the first being the cardiac flow; the second, the ratio of cardiac to myocardial flow. The myocardial flow is derived at this point from the two previous solutions. MacIntyre et al.5 presented the mathematical analysis related to measurement of cardiac output by the radioisotope method.

The adaptation of the two equations used in this study* are as follows:

\[
F_h = \frac{C_{eq} \times B.V. \times 12}{A_h}
\]

and

\[
\frac{F_c}{F_h} = R = \left(\frac{A_c}{A_h}\right)^2 \left(\frac{T_h}{T_c}\right)
\]

The first equation determines cardiac flow rate, and the second is an expression relating myocardial flow to cardiac flow.

\[
F_h = \text{Cardiac flow rate in liters per minute when the proper conversion factors have been applied.}
\]

\[
F_c = \text{Coronary flow rate, also in liters per minute.}
\]

\[
C_{eq} = \text{Background count rate in inches, which is proportional to counts per minute.}
\]

\[
B.V. = \text{Blood volume of the subject as determined either from statistical tables or the isotope-dilution method.}
\]

\[
12 = \text{A constant relating inches of paper travel to time in minutes (12 inches per minute).}
\]

\[
A_h = \text{Area in square inches under the portion of the curve related to cardiac flow.}
\]

\[
A_c = \text{Area, in square inches, related to flow in the coronary bed.}
\]

\[
T_h = \text{Time in inches or millimeters during which the area } A_h \text{ was created.}
\]

\[
T_c = \text{Time in the same units as } T_h \text{ during which the area } A_c \text{ was created.}
\]

\[
R = \text{Dimensionless number relating cardiac and coronary flow rates.}
\]

The tracings provide the measured data \(A_h, A_c, T_h, \text{ and } T_c\); along with the subject blood volume, they are necessary to produce \(F_h, F_c, \text{ and } R\). Areas \(A_h \) and \(A_c\) are measured with a planimeter. Other measurements are established by a scale.

Figure 1 is used as reference in describing the actual procedure. Since the recorders produce time-history plots with the beginning time on the right,
MYOCARDIAL BLOOD FLOW

the same plan is used in the sketch. Figure 1 represents the idealized tracing. The point a is the intersection of the cardiac flow curve with the beginning of the coronary flow curve. Because we know that at some future time the bolus must pass completely from the heart into the arterial system, we may extrapolate the remainder of the cardiac output curve. A first approximation might be to note that the blood must leave a closed vessel at the dotted line extending from point a to the base line. Two methods are put forward for developing the shape of the line. One is the mathematical approach of least squares, and the second is to use a curve that approximates the idealized extrapolation. Since the first system based on the curve shape is not very accurate and is time-consuming, the second system was adapted.

A similar treatment of the data at point b closes the area A_s. Figure 1 makes clear the methods used in gathering the time from the tracing.

Measurement of the background count level, Ceq, is oversimplified in the smooth tracing presented in figure 1. The technic applied in this study was to use a transparent straight edge and to estimate visually the area above and below the edge of the rule. When a balance of area was established, a line was inscribed on the tracing, and the height was recorded.

All of the required reduction data are now available for measure and when treated in the two formulas previously presented, the cardiac and coronary flow rates are obtained.

As in any testing procedure, this one on occasion produced records that were considered "invalid" or not analyzable. Criteria for discarding records consisted of two major items. The area could not be measured if a deflection went beyond the recording limits. Such an excessively large tracing could not be analyzed if the area loss exceeded 20 per cent, or if the distorted portion masked the points a or b. The second kind of record that was considered unsatisfactory was one in which the points a and b could not be detected.

Some tracings exhibited no large excursions or humps, and the background deflections were nearly as high as the initial major deflection produced by the appearance of the isotope in the right heart, or the femoral artery tracing had no characteristic rise.

These complete failures occurred in remarkably few instances. Six of the 47 subjects produced records that could not be analyzed, of which only one was due to over-amplification.

**Results**

The rate of blood flow in the average adult is approximately 5 liters per minute. Since the calculated blood flows ranged from a value less than 5 to over 25, it is doubted that this technic is of clinical value. This agrees with the findings of Shipley et al.

Due to the differences in individual rates of blood flow, the sample count rate, and the distance from the heart to the scintillation probe, no correlation was expected between the measured variables of area and time; however, it was hoped that the number R might

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Heart flow (L/min.)</th>
<th>Ratio of coronary flow to the heart flow</th>
<th>Coronary flow (L/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group (30)</td>
<td>11 (Av.)</td>
<td>8 × 10^4 (Av.)</td>
<td>0.9 (Av.)</td>
</tr>
<tr>
<td></td>
<td>18 (High)</td>
<td>25 × 10^4 (High)</td>
<td>3.6 (High)</td>
</tr>
<tr>
<td></td>
<td>6 (Low)</td>
<td>2 × 10^4 (Low)</td>
<td>0.2 (Low)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group (31)</td>
<td>11 (Av.)</td>
<td>9 × 10^2 (Av.)</td>
<td>1.1 (Av.)</td>
</tr>
<tr>
<td></td>
<td>22 (High)</td>
<td>27 × 10^2 (High)</td>
<td>4.2 (High)</td>
</tr>
<tr>
<td></td>
<td>4 (Low)</td>
<td>1.5 × 10^4 (Low)</td>
<td>0.1 (Low)</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(61)</td>
<td>11 (Av.)</td>
<td>8.4 × 10^2 (Av.)</td>
<td>1.0 (Av.)</td>
</tr>
<tr>
<td></td>
<td>22 (High)</td>
<td>27 × 10^2 (High)</td>
<td>4.2 (High)</td>
</tr>
<tr>
<td></td>
<td>4 (Low)</td>
<td>1.5 × 10^4 (Low)</td>
<td>0.1 (Low)</td>
</tr>
</tbody>
</table>
Simultaneous time-history recording of radiation activity as detected by scintillation probes positioned over the femoral artery and precordium following injection of RISA.

Discussion

Accuracy and Reliability of System

A great number of variables are involved in the results. Many areas of the laboratory procedure may be discussed, such as probe size, recorder response time, chest cavity dimensions, serum injection rate; but we will limit consideration to the test procedure and the data reduction process.

The Testing Procedure

Determination of the blood volume by serum dilution as used in most of the tests showed some scatter, but in only very few cases was the value so abnormal that a number was obtained from statistical tables for use in data analysis. The blood volume term is directly proportional to the blood flow rate in liters per minute from the heart in equation 1. Therefore, the small error encountered in blood volume determinations could not ac-
count for the gross error in cardiac output values obtained in this study.

The background count level (Ceq) is determined from the tracing after systemic circulation of less than 1 minute. In the blood volume procedure, a wait of some 15 minutes was allowed before the background sample was taken. No experimental evaluation of this effect has been made. Ceq is again introduced in the flow equation 1, in direct proportion to flow rate. This factor may contribute to the average large flow numbers in the test results; however, the correcting value will be more or less constant from subject to subject, and this would still leave us with a large scatter.

The Reduction Process

The shape of the tracings of count activity is expected ideally to appear very much like that of figure 1; however, the random nature of the count level of the radioactive tracer (fig. 2) is so large as to obscure the desired information. In electrical terms this can be expressed as signal-to-noise ratio. When the noise becomes as large as the signal, the probability of gaining information drops to less than half. It is possible to filter the noise out of the tracings, but the important information concerning the timing of points a and b (fig. 1) would be lost. The problem of noise, defined as unwanted signals, is of large magnitude, and probably accounts for much of the scatter of the results.

Furthermore, since the ratio of heart to coronary flow rates depends upon the square of these two areas, Aq and As, the determination of this ratio is even more variable than of the heart flow alone.

A note concerning other measured variables should be inserted in this discussion. The areas measured with the planimeter are accurate within 0.3 inch² and provide an insignificant source of error. The two values of distance measured as time of course, are susceptible to visual error, but this error is thought to be less than 1 per cent of the readings. This too, then, is an insignificant source of error. Similarly, the distance measure resulting in Ceq or background level is subject to a small error; however, the establishment of the inscribed line is subject to error of the order of 15 per cent and is a significant source of error.

Conclusions

The results presented here have a large scale error and a large scatter, so that we recommend that further clinical use of this method should not be attempted. If the coronary portion of the flow rate curve exists, then a change in the present instrumentation is needed to allow use of the technic of Sevelius and Johnson in defining a coronary portion of the flow rate.

An attempt is made to evaluate the possible source of errors.

References

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