Cardiac Output of Men and Dogs Measured by in vivo Analysis of Iodinated (I\(^{131}\)) Human Serum Albumin

By Rex L. Huff, M.D., David D. Feller, Ph.D., Oliver J. Judd, M.Sc., and George M. Bogardus, M.D.

A time-intensity analysis of I\(^{131}\) was carried out with a highly shielded well-collimated scintillation detector placed over the chest of normal men and women, patients and dogs. I\(^{131}\) human serum albumin solution was injected intravenously. The curves thus obtained when analyzed for cardiac output gave values not significantly different from simultaneously obtained direct Fick values.

The first published effort to record the intensity of radioactivity as a function of time over the heart following a single intravenous injection was by Prinzmetal and associates.\(^1\) They used a relatively unshielded Geiger tube and Na\(^{24}\). Despite relative insensitivity of Geiger tubes to hard gamma rays, they were able to detect (by in vivo analysis) two peaks of radioactivity representing the entry of Na\(^{24}\) to the right and left heart. Work of a very similar nature was published shortly after by Waser and Hunzinger.\(^2\) Their work also includes simultaneous measurements of the peripheral circulation.

This type of study has recently been made by Shipley and co-workers\(^3\) with modern scintillation equipment and wide angle counting of I\(^{131}\). A more extensive analysis of the data was made from the standpoint of the possibility of computing cardiac output, but the authors concluded that the method gave results roughly twice greater than those of conventional methods. They justify the use of a modified Hamilton equation with curves having the double rise on the basis that the equilibrium value truly represents the sum of the equilibrium values of the two components causing the double rise, that is, the radioactivity in the right and left sides of the heart. This leads to the assumption that the radioactivity of either of the waves does not reinforce the other. But this would tend to make the values for cardiac output too low and, therefore, is perhaps of little significance since their values were twice too high rather than too low. The major cause of the lack of correlation between their data with that of conventional methods for cardiac output is thought to be due to the inordinately high equilibrium value occurring due to the use of a wide angle counter. They discuss this possibility.\(^4\)

Perfect simulation of the conditions for use of the Hamilton equation\(^1\), \(^5\), \(^6\) for cardiac output on data obtained by external detection of gamma rays probably can never be achieved; however, the results of our studies correlate so well with the conventional direct Fick method that we think them worth reporting. The major modifications we have made from the preceding method,\(^3\) and which we feel contribute to the success of the technic, are (1) collimation with a 3/8 inch \(\times\) 2 inch orifice;\(^7\) (2) positioning of the counter on an area of the body where there is a relatively small or insignificant amount of intervening musculoskeletal blood; and (3) location near the aorta. The effects of these modifications in technic are discussed.

Methods

Isotope. Human serum albumin tagged with I\(^{131}\) was used routinely in amounts varying from 100 to 200 \(\mu\)c. When it was necessary to repeat the test immediately, 300 \(\mu\)c. were given as the second injection. In such instances, Lugols solution was administered during the subsequent week.
Apparatus. The scintillation detector consisted of a thalliated sodium iodide cylindrical crystal \(\frac{3}{4}\) inch high and \(\frac{3}{4}\) inch in diameter optically coupled to a photomultiplier tube. The detector was shielded by two inches of lead on all sides except for the \(\frac{3}{4}\) inch diameter cylindrical hole used to collimate the radiation. A cathode follower coupled the signal to either a scaler with a plug-in ratemeter or a rate-meter and/or scaler.

The method whereby the data were recorded depended on the driving units used. The output of the ratemeter registered on a potentiometer recorder and the output from the scaler was taken from the register driving impulse through a suitable voltage pulse shaping network and recorded on one channel of a galvamneter type recorder. The latter recorder gave a clear record of the register impulses when the paper speed was 2.5 cm. per second and the scaler was set to scale by 64. The potentiometer recorder had a paper speed of 180 inches per hour and its associated ratemeter had an integration time constant of 2.5 seconds. Both methods of recording could be used simultaneously. In order to evaluate the time constant of the ratemeter integration circuit and response of the recorder, a hand plotted histogram of the recorded register impulses of the scaler was prepared and compared to the pen written record. When a three second interval histogram was plotted, the integral under the primary circulation peak was not measurably different.

Evaluation of detector field. Positioning a point source showed that the angle at 30 degrees encompassed all of the high counting rates and that the rates fell off sharply; i.e., within 1 inch of the 30 degree solid angle. At three to four inches from the outer plane of the aperture, the diameter of the field is three and one-half inches.

Since the count rate of a point source falls off as the reciprocal of the distance squared while the "counted volume" increases with distance, an experiment was performed to evaluate the relative counting efficiencies of segments of a half-inch thickness and about 16 inches in diameter when present at different distances from the aperture. In this way it was possible to show that the layer of \(I^{131}\) solution nearest the counter contributed about twice as much as the layers between three and four inches away. The reduction in count rate with distance was roughly exponential with a half value of three inches.

Procedure of Injection. The human subject, seated and at rest for ten minutes prior to injection, had the detector placed on the skin between the first and second ribs or at the second rib at the left parasternal line and with the axis of the collimator forming an angle of approximately 10 degrees to the left side, posteriorly. The venopuncture was made using a 21 gauge needle mounted on an empty syringe. This syringe was removed and after a free flow of blood was assured, the syringe containing the \(I^{131}\) human serum albumin (in a volume of 0.1 to 1.0 ml.) was attached; injection was made in a single continuous motion and required about 1 second. In 5 to 10 minutes, two venous blood samples were taken for blood volume determination.

Direct Fick cardiac outputs. Fick methods were carried out in the usual manner on unanesthetized patients. Mongrel dogs in a healthy state were anesthetized with pentobarbital (30 mg. per K.) In some cases, the catheter was placed in the pulmonary artery while in others it was placed in the right ventricle. The cardiac output determinations by Fick and dilution technics were carried out simultaneously.

Calculation of flow rate. The initial fall in intensity of radioactivity following the first rise was extrapolated in the manner of other investigators. Extrapolation was done in the early studies on a hand plotted histogram from the data of the galvanometer type recorder, but in most of the studies the curves of the automatic pen writer were extrapolated directly on the recorder paper. The area under the primary extrapolated curve was measured with a planimeter in square inches. The area was divided by the length in inches which represented one minute since recorder speed was expressed in inches per minute. This quotient was then divided into the height in inches of the equilibrium value. Thus

\[
\text{Blood volumes per minute} = \frac{\text{Area} \times \text{inches}}{\text{Height} \times \text{inches}^2} \times \frac{\text{Recorder paper speed in inches per min.}}{60}
\]

The dimension of blood volumes per minute is valid if it is assumed that the ordinate values of the curve can be reliably related to the equilibrium value where all the injected dose \(I\) is diluted in the entire blood volume. This equation for computation of output differs from the formulation of Kinsman and associates, only in the fact that concentration \(C(t)\) is presented as \(C(t) = \frac{I}{BV(t)}\) and the equation for flow \(F\):

\[
F = \frac{I}{\int_{t_1}^{t_2} C(t) \, dt} = \frac{I}{\int_{t_1}^{t_2} \frac{1}{BV(t)} \, dt} = \frac{1}{\int_{t_1}^{t_2} \frac{1}{BV(t)} \, dt}
\]

where \(BV(t)\) is the time varying fraction of blood in which the injected dose \(I\) is apparently diluted, and the time limit \(t_2\) is the apparent termination of the extrapolated curve. Shipley and associates discuss this derivation in a slightly different form.

\[
\text{Area (inches)}^2 \frac{\text{of extrapolated curve}}{\text{recorder paper speed in inches per min.}}
\]
RESULTS AND DISCUSSION

The majority of the curves show only one major rise and fall in counting rate with time (fig. 1). These eight graphs are smoothed curves made from the three second interval histograms of eight normal subjects. The equilibrium value obtained after 3 to 10 minutes is also shown. The curves are similar to those obtained by direct arterial sampling.8,9,10 About 20 per cent of these curves exhibited a double rise when one second interval histograms were plotted. They have some resemblance to the doubly peaked in vivo curves published by others;11,12 however, the decrease in counting rates between the two peaks was less. Cardiac output calculated with either the one second interval curve or the three second curve was the same.

Table 1 gives the data of 28 normal women and 36 normal men. The age range was 17 to 57 years but most subjects are between 20 and 40 years. The mean cardiac index for the women was 3.3 L. per minute per square meter of body surface area with a standard deviation of 0.8; while the mean and standard deviation for the 36 men were 3.6 and 0.8 L. per minute per square meter of body surface area respectively.

The range of the average of Fick cardiac indices reported by various investigators is from 3.27 to 3.79,11,17,14,16 and the range for the direct dye method is 2.85 to 4.19 L. per minute per square meter of body surface area.16,17,18 The mean cardiac index for the men and women by the in vivo method is 3.5 with a standard deviation of 0.8.

Table 1 also shows the calculated blood volumes of the subjects as well as the cardiac output in terms of blood volumes per minute. It is thought important, that these values are obtained as part of this method, since the former is useful information in the case of many cardiace and the latter is a parameter of blood turnover rate. The parameter of blood turnover rate, although not a true representation of all segments of blood in the body, is a general indi-

<table>
<thead>
<tr>
<th>Patients</th>
<th>Fick L/min./M²</th>
<th>I° HSA in vivo L/min./M²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. RIT</td>
<td>2.05</td>
<td>2.04</td>
</tr>
<tr>
<td>2. SHI</td>
<td>2.11</td>
<td>2.14</td>
</tr>
<tr>
<td>3. HAN</td>
<td>2.69</td>
<td>2.80</td>
</tr>
<tr>
<td>4. MAC</td>
<td>2.75</td>
<td>2.66</td>
</tr>
<tr>
<td>5. SAN</td>
<td>1.60</td>
<td>1.53</td>
</tr>
</tbody>
</table>

* Mean.
† Standard deviation.

Table 1.—Cardiac Output Values

![Graph](https://example.com/graph.png)

**Fig. 1.** Data from eight normal subjects, obtained by a crystal detector well-collimated and shielded, placed at the level of the second rib at the left parasternal border. Ordinates show the count rate divided by 64 at successive three-second intervals. Short horizontal line is the equilibrium level obtained after several minutes of measurement. Dashed line is the extrapolation used for measurement of the area under the curve, abscissae, time in seconds.
cation of blood mixing efficiency. Inspection and analysis of the individual curves demonstrate the approximate volumes and rates of slowly mixing components. This type of analysis constitutes the subject of another study.

Table 1 allows comparison of seven simultaneous Fick and in vivo isotope determinations (5 patients). These paired data with the exception of one (patient with very low output) are almost identical. The mean of the differences of the paired data is 0.072 L per minute per square meter; while the standard deviation is 0.19 and the standard error of the mean 0.095. The "t" value is thus 0.7(52 and 53) and the corresponding "p" is equal to or greater than 0.5.

The accuracy of detector positioning on the chest is limited in several ways. The contour of the chest may have an irregular outward convexity in the region of the first and second ribs so that placing the axis of the collimator normal to the skin surface, while directing the axis perpendicular to the anterior topographic projection of the arch of the aorta, is impossible. In such an instance the detector was always placed with respect to the expected aortic projection based on location of bone prominences.

Although efforts were made to effectively isolate a segment of the vasculature so it alone would be in the radiation detector field, it is not thought that this is mandatory to the success of the method. That it is not necessary to "effectively isolate" certain volumes is true for the chambers of the heart and great vessels, but not for the various distal vascular beds. This fact was realized by Shipley and co-workers* and pointed out as justification for examination of their doubly humped curves by the Hamilton equation. Veall and associates,' have presented a mathematic proof for this contention. As pointed out above, such an application cannot be made to in vivo data which represent a large portion of some distal segment of the circulation, for example, musculoskeletal circulation. Thus the tissue nearest the detector, the intervening body wall, falls into this category. Thoroughgoing consideration of the effect of coronary blood flow on these measurements cannot be made at this time because of lack of data.

Table 2 presents data of simultaneous Fick and in vivo I" cardiac output in dogs. The average absolute difference of the two methods of 22 trials in 12 dogs was 12 per cent. The mean of the differences of the paired data is 46 ml per minute; while the standard deviation is 531 and the standard error of the mean is 116 ml per minute. The "t" value is thus 0.397 and the corresponding "p" is equal to or slightly greater than 0.7. The correlation coefficient was .90 with a high degree of significance. Although the animals were under deep anesthesia, their blood turnover rate was several blood volumes per minute, in contrast to slightly over one blood volume per minute in man.

That the I" data of the dog studies differed so slightly from the Fick dog data was surprising in view of the difficulty of accurate counter localization and the use of a counter.

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**Table 2.—Dog Data: Simultaneous Cardiac Output Determinations by the Direct Fick and in vivo I/* HSA Method**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Trial</th>
<th>Wt. Kg.</th>
<th>A-V Diff. %</th>
<th>On Consum. cc.</th>
<th>BV (cc.)</th>
<th>Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fick cc./ min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BV/ min.</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>10.0</td>
<td>6.68</td>
<td>57</td>
<td>650</td>
<td>583</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>16.5</td>
<td>2.66</td>
<td>138</td>
<td>1250</td>
<td>5400</td>
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<tr>
<td>3</td>
<td>4</td>
<td>13.6</td>
<td>2.21</td>
<td>70</td>
<td>935</td>
<td>3180</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>12.1</td>
<td>3.22</td>
<td>82</td>
<td>607</td>
<td>2540</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>17.6</td>
<td>2.61</td>
<td>120</td>
<td>4510</td>
<td>5150</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>10.4</td>
<td>4.52</td>
<td>73</td>
<td>713</td>
<td>1630</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>5.19</td>
<td>81</td>
<td>713</td>
<td>1580</td>
<td>1800</td>
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<tr>
<td>12</td>
<td>13</td>
<td>10.4</td>
<td>4.40</td>
<td>80</td>
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<tr>
<td>14</td>
<td>15</td>
<td>3.54</td>
<td>94</td>
<td>815</td>
<td>2690</td>
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<tr>
<td>15</td>
<td>16</td>
<td>19.8</td>
<td>5.00</td>
<td>94</td>
<td>1080</td>
<td>1580</td>
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<tr>
<td>16</td>
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<td>16.5</td>
<td>1.36</td>
<td>53</td>
<td>1545</td>
<td>3000</td>
</tr>
<tr>
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<td>19</td>
<td>11.0</td>
<td>2.00</td>
<td>62</td>
<td>1200</td>
<td>3100</td>
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<tr>
<td>19</td>
<td>20</td>
<td>19.0</td>
<td>5.65</td>
<td>93</td>
<td>1092</td>
<td>1640</td>
</tr>
<tr>
<td>21</td>
<td>22</td>
<td>14.0</td>
<td>2.00</td>
<td>50</td>
<td>934</td>
<td>2575</td>
</tr>
<tr>
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<td>10.0</td>
<td>2.00</td>
<td>50</td>
<td>934</td>
<td>2570</td>
<td>2550</td>
</tr>
</tbody>
</table>

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having the same collimation as in the human studies. The similarity of the data gathered by these two methods leads us to conclude that for men and dogs the body surface measurements of $^{131}$I are a good approximation for a real arterial curve. We believe the chief reasons that the in vivo method described here gives values similar to the direct Fick method and the direct arterial sampling are:

1. The early and main portion of the curve is produced by tagged blood in the major fixed vessels. The isotope in pulmonary artery and veins, as well as their branches and tributaries probably contributes slightly to the initial curve. The position used (second rib at the left parasternal line) assures us that in most individuals studied, the major "sampled" vessel is the aortic arch. The theory, developed and mentioned above, suggests that pure single vessel sampling is not required.

2. The equilibrium value is measured over a very small portion of a relatively avascular bony area. The results of the two experiments described under "Methods" indicate the relative efficiency of counting tagged material at different distances from the outer plane of the orifice. The detected field in the mediastinum is nearly 100 per cent blood while that of the thoracic wall is only about 2 per cent blood. Thus if one considers a core of musculoskeletal system 2 cm. × 3 cm. or about 10 cm$^3$, there is not likely to be more than 0.6 cm$^3$ of blood present or about 1/100,000 of the total radioactivity in the body. The value 0.6 cm$^3$ is high; it is more likely in the order of 0.2 to 0.4 cm$^3$ since musculoskeletal parts containing large quantities of fat or bone contain a lesser amount of blood. The position at the second rib near the midline has the advantage that it rarely, if ever, has a large thickness of fat or musculoskeletal tissue.

Almost simultaneously with our first presentation of the results of this method, Veall and co-workers reported a nearly identical method with comparable results. Through a personal communication from N. Veall, we learned that other investigators have obtained additional data confirming the reported similarity of the results of the in vivo isotope and direct Fick methods.

This in vivo method has several advantages, chiefly its simplicity. The subject may be readily studied in recumbent, erect or sitting positions. Except for marked uncontrollable chest movements, there are few abnormalities of the subjects which interfere with this procedure; it also gives additional useful information on blood volume and cardiac output in terms of blood volume per minute.

The test may be repeated as indicated without exceeding the tolerance dose if no more than 0.3 μc. is present in the body and Lugols solution is given to block the uptake of $^{131}$I by the thyroid. The 300 μc. value is calculated for total body distribution of $^{131}$I. It is somewhat less than the value of 8.3 μc. per Kg. given by Marinelli and co-workers, which results in 0.1 Roentgen equivalent physical representation during the first day following the deposition.

**SUMMARY**

A method for estimating cardiac output by external body counting of $^{131}$I following a single injection of $^{131}$I is described. A well-collimated and shielded scintillation detector was placed at the left parasternal line between the first and second ribs for recording a time concentration curve. Calculation of cardiac output was by a modification of the Hamilton dye method. Seven patient and 22 dog studies, carried out simultaneously by this method and the direct Fick method, when subjected to the "t" test, showed the means not to be significantly different. Sixty-four normal subjects studied by the external counting technic had a mean cardiac index very similar to published values obtained by conventional methods for normal subjects. This method has the advantage of simplicity in application. Serial arterial blood sampling is not required.

**ACKNOWLEDGMENT**

We are indebted to Doctors J. Michel, Belding H. Scribner and J. Thomas Payne for their assistance in cardiac catheterization. The constant encouragement and assistance of Dr. Robert S. Evans was of great value.
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Circ Res. 1955;3:564-569
doi: 10.1161/01.RES.3.6.564

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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