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

II. Clinical Studies

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A method previously described for the determination of cardiac output by the injection of iodinated (I\(^{131}\)) human serum albumin has been extended to a study of its application to patients. A technic suitable for clinical use has been described and values obtained have been compared with those simultaneously determined by cardiac catheterization. The average deviation from Fick principle values was ±8.3 per cent over a range from −8.4 per cent to +18.7 per cent. Certain precautions in technic necessary for accuracy have been stressed.

In an attempt to develop a convenient, accurate method for cardiac output determination which can be used at fairly frequent intervals over periods of days, weeks, or months, rather than during a few hours, the blood dilution principle of Stewart\(^1\) and Hamilton\(^2\) has been adapted for the use of tracer doses of I\(^{131}\) attached to human serum albumin. The radioactivity of the arterial blood concentration has been measured by a scintillation counter as blood is flowing over the counter and the dilution curve continuously recorded by a Berkeley counting rate computer, used in conjunction with a scaler and Esterline Angus graphic meter.

The experimental details of the necessary instrumentation and technic were studied first in dogs, and previously reported.\(^3\) It was found that the cardiac output determined by this method showed an over-all agreement of +9 per cent with values simultaneously determined by an optically recording aortic flow meter if allowance was made for the unmeasured coronary flow in the rotameter values. For details of the recording apparatus and calculations involved in this method, the previous work should be consulted.

The purpose of this paper is to describe the use of this modification of the dilution principle in humans and to compare the results with the values derived from simultaneously determined Fick outputs, using the cardiac catheterization technic. In previous animal work, the dilution and rotameter outputs were determined simultaneously for identical temporal periods. In using the Fick principle in humans, exact simultaneity was not possible, since determination of oxygen consumption required usually 4 to 6 minute periods, whereas dilution curves were usually inscribed within a 20 to 50 second period. Although a handicap, it is thought that inherent differences in the use of the methods have not detracted seriously from the data obtained.

Technic

The general procedure of technic followed in these studies was similar to that previously reported.\(^3\) Figure 1 represents a block diagram schema of the technic. Into either brachial or femoral artery was inserted a Courmand No. 18 arterial needle after infiltration with 2 per cent procaine. This has usually been a perfectly painless procedure, if care is taken to infiltrate sufficiently around the artery. The needle was so adjusted within the arterial lumen that a free, pulsatile flow existed when the stylette
was removed. This was a necessary precaution, and unless this free, pulsatile flow could be maintained, the needle was removed and reinserted.

A stainless steel tube of 2 mm. bore, curved to fit closely over the counter crystal, was used to lead blood past the counter. The inner surface was siliconized to aid in clot prevention. Rubber tubing was attached to both ends of the steel tubing, for leading blood from the needle, and for collecting blood in a beaker after it had passed the counter (fig. 2). This steel tube and counter were completely shielded by lead bricks 1\(\frac{1}{2}\) inches thick and placed in a suitable unit to insure stability when used. Prior to each determination, a small amount of saline containing heparin was flushed through this external flow system. To record the curve of dilution, it was necessary merely to connect this system to the arterial needle, and when blood was dripping freely into the beaker, the calculated volume of tagged albumin was rapidly delivered into the circulation. As soon as definite recirculation was identified on the tracing, the flow was stopped, and the system disconnected from the arterial needle and flushed with tap water until clear. This flushing procedure has been found to eliminate completely any radioactive residue. After a 10-minute interval, the system was reconnected to the arterial needle, and blood allowed to drip slowly into test tubes for measurement of the final concentration of radioactivity in the blood for determination of the blood volume. The final dilution of the radioactivity in the blood was taken simultaneously as it passes through the flow system in order that the system may be calibrated in terms of the blood volume. The mean dilution during the period for the primary circulation as related to the final dilution indicates what portion of the total blood volume flowed during this time. The measurement of the total blood volume therefore permits calculation of the cardiac output in terms of volume per period of time (liters per minute). The complete analysis is given in detail in the previous publication which shows that the cardiac output by the dilution method may be expressed by the equivalent expression:

\[
F = \frac{C_f}{C_{ar}} V \frac{1}{T}
\]
where $F$ is the cardiac output in terms of volume per unit time, $C_f$ is the final concentration, $C_{av}$ is the average concentration, $V$ is the blood volume and $T$ is the period of first circulation flow. Typical output curves are shown in figures 3 and 4. It can be seen that the primary dilution curve in figure 3 is tall and narrow as contrasted with figure 4. Calculations show that the cardiac output in figure 3 is 28 per cent greater, whereas blood volume is 9 per cent less than in figure 4.

Injection of the tagged albumin was made either through the catheter or into an arm vein through a No. 18 gauge needle. If given through the catheter, the injection was immediately followed by rapid flushing with 15 to 20 cc. of normal saline. Flushing of the needle in the peripheral vein was also carried out on these patients. In subsequent studies, it was found, however, that flushing is not necessary if the volume of isotope is kept reasonably large (3 to 4 cc.). Arm positioning is of importance in that there must be rapid delivery of the material into the right heart. Significant obstruction to free flow may result from incomplete relaxation of the upper arm and shoulder girdle and excessive abdution or outward rotation.

For a period of 24 hours before and continuing for 24 to 72 hours following the study, Lugol’s solution, 10 drops three times daily, was administered to minimize the uptake of the dissociated $^{131}$I by the thyroid gland.

Procedure

Patients from the medical wards were studied in the morning before breakfast following an 8 to 10 hour night’s rest. Sodium seconal, 0.1 Gm., was given approximately 45 minutes before cardiac catheterization was begun. Following the placing of the catheter in the right heart or pulmonary artery, the arterial needle was inserted into either the femoral or brachial vessel. After a rest period of 20 to 30 minutes, cardiac output was determined by both the Fick principle and dilution method as nearly simultaneously as possible; arterial and venous blood samples were drawn, the determination of oxygen consumption begun, and tagged albumin rapidly injected. Following the initial dilution curve, a second set of arterial and venous samples was usually drawn for oxygen analysis. If the Sanborn metabolator was used, oxygen consumption was started after the injection of the curve. If two sets of blood samples were drawn, the A-V differences were usually averaged, unless the interval between samples was excessive, in which case the set drawn nearest to the recorded dilution curve was used. In one instance, an arterial needle was inserted into two arteries and arterial and mixed venous blood was drawn during the dilution determination. No apparent greater accuracy was obtained in this one study and because of the inconvenience, the sequential procedure was preferred.

Oxygen content of blood was determined either by Van Slyke analysis or by the spectrophotometer method of Hickam, or by both. Oxygen consumption was calculated from the slope of curve of the utilization in the Sanborn clinical metabolator in 10 patients and in two patients by collection of expired air in a Tissot apparatus with oxygen analysis performed by the Pauling gas analyzer.

**Results**

Out of 15 attempts, there were 12 single satisfactory runs on 11 patients from the technical standpoint of both procedures. Three were unsatisfactory and will be discussed separately.

The table gives the data upon which the calculations were based, catheter position in the right heart, amount and route of iodinated albumin administered in addition to the blood volume, cardiac outputs and the percentile deviation of the dilution from the Fick output.

The range of deviation was from $-8.4$ per cent to $+18.7$ per cent with an average deviation of $\pm 8.3$ per cent. These studies are in substantial agreement with previously reported studies using T-1824 dye as the diluted material. Also to be noted is the large range of outputs exhibited by these patients, which vary from 2.83 liters per minute in run number 5 in a patient with moderately severe chronic congestive heart failure, to 11.45 liters per
minute in run number 10 on a patient recovering from acute alcoholism. Agreement in values was good over the range of outputs studied.

In comparing studies 4 and 5, which constitute two separate determinations 21 days apart on the same patient, the absolute decrease in output as shown by each was approximately the same, 0.75 liters per minute by the Fick and 0.57 liters per minute by the employed can be used to calculate accurately the cardiac output.

The radioactivity of the injected iodinated (I^131) human serum albumin was kept to the minimum amount that was still sufficiently high to give reasonable counting rates. This was found to be in the range of 120 to 160 μC, giving a final dilution concentration of 0.02 to 0.03 μC per cubic centimeter.*

| Table 1.—Summary of Data on Which Calculations Were Based in 12 Successful Studies |
|---|---|---|---|---|---|---|---|---|---|---|---|
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | F.P. | Alcoholism | 18.3 | 14.6 | 3.7 | 255 | R.V. | Cath. | 150 | 5.18 | 6.90 | 6.57 | -1.8 |
| 2 | T.J. | Diabetes | 19.0 | 15.5 | 3.5 | 280 | P.A. | Cath. | 154 | 5.76 | 8.00 | 8.80 | +10.0 |
| 3 | H.T. | Cancer of lung | 8.4 | 4.5 | 3.9 | 235 | P.A. | Cath. | 135 | 5.55 | 6.02 | 7.00 | +17.0 |
| 4 | N.L. | A-V fistula | 17.9 | 13.3 | 4.6 | 165 | R.A. | Cath. | 147 | 5.17 | 3.58 | 3.92 | +9.5 |
| 5 | N.L. | A-V fistula | 18.8 | 12.8 | 6.0 | 170 | R.A. | Cath. | 134 | 5.04 | 2.83 | 3.35 | +18.7 |
| 6 | W.C. | Arteritis | 19.1 | 15.55 | 3.55 | 210 | R.A. | Cath. | 143 | 4.84 | 5.92 | 5.95 | +0.5 |
| 7 | R.B. | Susp. axillary | 17.3 | 13.4 | 4.0 | 270 | R.A. | Cath. | 159 | 4.33 | 6.75 | 6.27 | -7.1 |
| 8 | G.G. | Convalescent | 17.0 | 11.8 | 5.2 | 240 | R.A. | Cath. | 146 | 5.74 | 4.62 | 5.38 | +16.5 |
| 9 | F.M. | Convalescent | 16.8 | 13.5 | 3.3 | 378 | R.A. | Periph. vein | 145 | 6.57 | 11.45 | 11.30 | -1.3 |
| 10 | C.W. | Convalescent | 13.0 | 9.7 | 3.3 | 199 | P.A. | Periph. vein | 142 | 5.89 | 6.00 | 6.28 | +4.6 |
| 11 | L.G. | Syphilitic heart | 16.4 | 11.8 | 4.6 | 275 | R.A. | Cath. | 147 | 6.11 | 5.98 | 5.48 | -8.4 |
| 12 | I.J. | Emphysema | 15.4 | 9.9 | 5.5 | 172 | P.A. | Periph. vein | 140 | 5.18 | 3.13 | 3.16 | +1.0 |

Average: ±8.3

The dilution technic, giving relative decreases of 20.9 per cent and 14.5 per cent respectively.

**Comment**

Although the details of the technic, such as time of drawing bloods, placing of catheter tip, site, and type of injection of the iodinated protein varied somewhat, it appears that no consistently demonstrable errors were introduced, since, in general, satisfactory agreement of the dilution method with the Fick principle was obtained. Both methods are theoretically sound and this clinical study supports our previous conclusions from animal work, that the curves of blood dilution of tagged albumin recorded by the apparatus and technic employed can be used to calculate accurately the cardiac output.

The advantage of the higher concentration is that it is possible to record a greater number of points of concentration per unit time. At the concentrations used, a point was recorded every one or two seconds. This is at a slower rate than previous determinations, but was considered sufficiently adequate to describe the dilution curve. In addition to the dilution curve, the only other data required are the

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* A modification has recently been made to incorporate a thallium-activated sodium iodide crystal rather than an anthracene crystal as the detector. The greater detection efficiency will then enable either a smaller dose to be given or a higher counting rate to be obtained and subsequently more points recorded on the curve.
final concentration for calibration of the flow and the blood volume.

Difficulties with obtaining these data have been minor, although precautions have been found necessary in the delivery of the dose. This dose has been given in volumes of from 2 to 5 cc., which offers a fair compromise between being small enough to effect delivery within a short period of time and large enough to make error in delivery relatively small. The syringe used was calibrated in terms of output for one stroke and this output insured by fitting a double stopcock to the syringe and following the injected radioactive albumin with a 15 to 20 cc. flushing of normal saline solution.

Although care is taken during this injection, occasionally all the radioactive material is not inserted into the vein, but lies subcutaneously at the site of injection. It has become routine to check for any radioactivity remaining in the arm by placing the detector over this area and comparing it with the counting rate over the arm not given the injection. After these steps had been taken, very little difficulty has been encountered with the blood volume determination. A spot check has been made by comparing a simultaneous determination with the "blue dye" method which showed a deviation of less than 6 per cent. Two separate determinations on one patient (runs 4 and 5) by this method have shown a deviation of less than 3 per cent.

Loss of radioactivity in the blood drained off during the initial recording of the curve may theoretically affect the final blood volume calculation, if the drained blood contains a large proportion of the injected dose. However, with the small blood loss (30 to 50 cc.), only a minor difference is possible. In run number 2 the average concentration of the blood drained off into the beaker was about 30 per cent higher than the final dilution. For 50 cc. of blood removed this loss of injected activity corresponds to an error in blood volume of 15 cc., or 0.3 per cent.

In three patients, agreement was poor. In one, the Fick output of 3.3 liters per minute was recorded as 2.08 liters per minute by the dilution method, but partial clotting had occurred in the arterial needle and free flow through the system never obtained. Previous controlled studies in animals had shown that good arterial flow is necessary or falsely low output values will result from radioactivity diffusion within the stagnant segment of blood over the recording counter. In another, 2 cc. of tagged material was injected into the catheter without flushing. With the large catheter dead space, a smaller amount than used in the calculations was actually delivered, giving a falsely high value for the blood volume. In the third patient, the Fick output was 3.5 liters per minute as compared to a dilution output of 6.2 liters per minute. Technical difficulties with blood analysis and oxygen consumption gave reason to doubt the validity of the Fick output.

We have not attempted duplicate data or serial determinations in these patients, although this has been done in animals. At the time of this study, sufficient counter sensitivity had not been obtained to enable duplicate measurements to be performed easily and safely.

It should be emphasized that the technic for the determination of cardiac output by this method is easily and speedily performed and that curve analysis can be delayed for later calculation at one's leisure, if necessary.

Conclusions

1. A method for measuring cardiac output in man by a continuous recording system utilizing the injection of iodinated human serum albumin has been described.

2. Values obtained show an average agreement with those determined by the Fick principle of ±8.3 per cent over the range of outputs studied.

3. Certain sources of technical error, which may invalidate the determination, have been stressed, the major of which are maintenance of "free" flow during the recording of the primary curve, and accurate delivery of the injected dose upon which calculations are based.

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REFERENCES

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