Successive Measurements of Cardiac Output by External Monitoring Using Digital Counter and Automatic Digital Printer

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The selection of a calibration time for an external radioisotope determination of cardiac output is discussed with respect to obtaining values which agreed well with those of direct arterial sampling technique. Placement of external detector was also examined using 2 scintillation head with different collimators and focusing angulations simultaneously. External cardiac output demonstrated higher value by conventional 10 minute calibration method than 5 to 3 minute ones, and the values calibrated at 5 minute after RISA injection were in most reasonable agreement with those of direct value, and the authors recommended the left cardiac apex monitoring with 5 minute calibration as the standard method. Examples of successive determination of cardiac output before and after aminophylline injection are illustrated, along with a presentation of newly devised digital counter and automatic digital printer which are convenient for such serial determination. Response to the aminophylline was different between the normal individuals and the patients with heart failure. The utilization of the method presented may add an important clinical examination of cardiac function.

The methods most widely used to measure cardiac output are based either on the Fick or on the Stewart-Hamilton principle.

Fick method requires cardiac catheterization and can rarely be performed more than once on the same subject. The conventional Hamilton method using T-1824 as the indicator can also rarely be performed more than twice on the same subject because of its skin coloration. However, successive determinations of cardiac output at short

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intervals are requested to examine the cardiac function more clearly. In the original Hamilton method, after an indicator is injected intravenously, the arterial concentration of the indicator should be measured as a function of time by drawing the blood samples every one to 2 seconds for about one minute. Then the feasibility of estimating cardiac output from precordial dilution curve using radioactive materials was first suggested by Prinzmetal and coworkers. Subsequently, Shipley and associates gave estimates of blood flow, though the values obtained by them were twice as great as those of conventional methods, using scintillation equipment and wide angle collimator to record radiocardiogram. In Japan, Ueda and coworkers have also used radiocardiography in 1954, using radioactive sodium ($^{24}$Na), for the study of pulmonary circulation. Huff and MacIntyre, Pritchard and his coworkers have made refinements in the technique of the external determination of cardiac output, using radioactive human serum albumin (RISA) tagged with $^{131}$I, and gave estimates of flow which approximated those obtained by other methods. Thus the usefulness of an isotope dilution technique with external body counting in determination of cardiac output has been demonstrated for several years by many other authors. In Japan, appraisal of this method has been carried out in our radioisotope laboratory at first, and this test is now going to be used in many hospitals and radioisotope laboratories.

The following study was undertaken to evaluate 3 calibration times and different collimators by comparing the precordial method with direct arterial sampling method, and to extend the method to the successive measurements within short intervals using newly deviced digital recording apparatus of our own.

**Materials and Methods**

**Equipment:**

The scintillation counter used in this study has been described previously. As shown in block diagram of Fig. 1 and Fig. 2, 2 detectors and 2 scalers were used and the changes in radioactivity were recorded simultaneously. Both the recording system using galvanometer-type pen recorder and the other system using new apparatus were used in this study.

Fig. 3 shows the dimensions and efficiency characteristics of 3 collimators tested. Two scintillation heads placed on the left and right precordium respectively were used simultaneously throughout the studies. One scintillation head was focused over the apex of the heart and the other over the right sternal border at the 4th intercostal space, and both of these methods were examined making a different focusing angulation against the horizontal plane, so that left and right ventricles should be viewed predominantly (Fig. 2B, Fig. 10).
Digital Counter and Automatic Digital Printer:—

Pulses from the 2 photomultiplier pass through the pulse height analyzer

Fig. 1. The arrangement of apparatus for determination of radioactivity of the cardiac region after intravenous injection of $^{131}$I albumin.

Fig. 2. A: Scintillation counters. B: Position of patient in laboratory and the detectors placed over the right and left precordium at the same time. For correlation, a peripheral artery was used as the site of drawing samples.
to eliminate the low energy scattering $\gamma$ rays, and the remainders were recorded automatically every one second by digital counter and automatic digital printer.

Fig. 3. Dimensions and efficiency characteristics of 3 types collimators representing A (high), B (middle) and C (moderate) collimation. Every collimator was used in the correlation study and B collimator is utilized now for the routine standard study.

Fig. 4. A: Digital counter. B: Automatic digital printer.

This machine was deviced and produced through Oki Electric Industry Co. in Japan in cooperation with our laboratory. The photograph and the block diagram of this recorder are illustrated in Fig. 4 and 5. The circuit involved in this recorder performs several functions. It counts the number of pulses entered during the gate is open, and prints it automatically in succeeding short period. Four sets are arranged for the purpose of several radioisotope study (Table I). The first set of Table I was used in this study and radioactivity could be recorded automatically every one second successively as illustrated in Fig. 5 B. Pulses are counted for 0.6 second when the gate is open, representing one hundredth counting rate per minute, and then automatic digital printer makes a rapid printing within following 0.4 second. When a high background is present or successive examination is needed, the operation of the complement selector can remove the influence of these elevated counting rate upon the final reading by shifting the starting level down below zero, and one can read
directly the necessary counting rate which is free from background counts. This operation is also described in block form in Fig. 5 A. When counting rate is too high and exceeds the full scale of digital counter, conventional scaler placed before this counter (Fig. 1), consisting of 3 EIT tubes, is used to transmit pulses after the collection of predetermined number 10, 100 or 1000 counts, thus operating the function as a rate down unit. If the changes in the radioactivity are prerecorded on the tape and played directly into the input terminal of this digital counter at one tenth slower speed, every 0.1 second counting of the original phenomena is also possible by this machine and even the rapidly changing dilution process by every cardiac cycle can be recorded.16)

**Materials:**

The materials consisted of 37 cases, including 10 normal subjects, 13 patients

<table>
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<tr>
<th></th>
<th>Gate open (counting)</th>
<th>Gate closed (printing and resetting)</th>
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<tr>
<td>1</td>
<td>0.6 sec.</td>
<td>0.4 sec.</td>
</tr>
<tr>
<td>2</td>
<td>1.0 sec.</td>
<td>1.0 sec.</td>
</tr>
<tr>
<td>3</td>
<td>30.0 sec.</td>
<td>0.5 sec.</td>
</tr>
<tr>
<td>4</td>
<td>60.0 sec.</td>
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with heart failure, 10 with liver cirrhosis 2 with anemia and 2 with hyperthyroidism.

Procedure:

The examination was carried out in a fasting and resting state in a supine position. Two scintillation heads with different collimators and various focusing angulations were focused respectively over the right and left side of the heart simultaneously as described above. The $^{131}$I labeled human serum albumin containing 20 to 50$\mu$C of radioactivity was rapidly injected into the cubital vein and the dilution curves were recorded over the precordial region. At the same time, the blood samples were continuously drawn from the brachial or femoral artery in all cases and the cardiac output was directly calculated by Stewart-Hamilton method. The values obtained by this direct technique were compared with those of external technique in each case (Fig. 6). Blood samples were also taken at 3, 5 and 10 min. after the injection in order to calibrate the external dilution value against the blood dilution value. Cardiac output by external method was calculated at each point of these 3 calibration periods by using the equation (3) in Fig. 7 and was compared with the direct values.

Reproducibility of this method was also examined on subjects in a resting
state without giving any medications, then the effect of aminophylline was studied in 6 cases including 3 cases of heart failure. The measurements of cardiac output were performed repeatedly one to 3 times within 15 to 25 minutes after the intravenous injection of 250 mg. of aminophylline.

**Results**

1) Analysis of calibration time

In external counting method, both the right and left external dilution values were calibrated at 3, 5 and 10 minutes after the injection of RISA using blood samples taken at the same time. Thus 6 calculated values were obtained for each determination. Variations of calculated cardiac index against 3 calibration periods are illustrated in Fig. 8. In control group, most cases show larger values by 10 minute calibration method than those obtained by 3 or 5 minute method. The percent changes (mean value of these cases) are shown below. Such tendency was not found in cases of heart failure, and the mean values at these 3 calibration times were almost equal to each other. In Fig. 9, mean values of the variation of blood and external dilution values at each calibration time of these cases are shown as percent change taking 5 minute value as 100%. It can be presumed that if a relatively complete mixing is reached in an early stage after RISA injection, the ratio

\[
\text{Cardiac Output} = \frac{\text{R.I. injected \times 60}}{\int_0^t \text{Cdr} \, dt} \quad \ldots (1)
\]

\[
= \frac{1 \times 60}{(A+B) \times K} \quad \ldots (2)
\]

\[
= \frac{1 \times 60}{(A+B) \cdot \text{Blood Dilution Value} + \text{External Dilution Value}} \quad \ldots (3)
\]

\[
A = \text{planimetrically determined}
\]

\[
B = \int_0^t \text{Co} \, \text{dt} = \frac{C_t}{K}
\]

\[
A = \frac{B \cdot 602 \times 15}{t_1/2}
\]

\[
t_1/2 = \text{half time of Co}^{-1} \text{- curve}
\]
Fig. 8. Variations of calculated cardiac index by different calibration period (3, 5 or 10 min.). Note that cardiac index calibrated at 10 minute showed higher value than 3 or 5 minute’s one.

Fig. 9. Variations of both external and blood dilution value against calibration time. Note that external dilution value of control cases does not decrease parallel with the blood dilution value.
of the blood dilution value to the external dilution value should be constant throughout the following period. Our observations, however, demonstrated that in the period from 5 to 10 minutes the external dilution value showed little decrease, or in some case it even showed an increase, whereas the blood dilution value continued to decrease (Fig. 9). On the other hand, in heart failure both of them showed a sharp and parallel decrease in this period (Fig. 9). Comparisons of the values by the external method at different calibration times with those of the direct arterial method are presented in Table II. As seen in Table II, the

<table>
<thead>
<tr>
<th>Calibration period (min.)</th>
<th>3</th>
<th>5</th>
<th>10</th>
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<tbody>
<tr>
<td>Left external (L./min./M²)</td>
<td>+0.21 ± 0.39</td>
<td>+0.16 ± 0.22**</td>
<td>+0.44 ± 0.56</td>
</tr>
<tr>
<td>Right external (L./min./M²)</td>
<td>+0.32 ± 0.24</td>
<td>+0.23 ± 0.33</td>
<td>+0.55 ± 0.32</td>
</tr>
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* The data obtained from 13 cases, including 9 normals and 4 cardiacs
** Significant difference compared to 10 min. value

eexternal value of cardiac index showed positive systemic deviation to the direct value; however, the values calibrated at 5 minutes indicated minimal deviation and well correlated to the direct value.

2) Collimation and placement of the scintillation head

Three tapercone collimators shown in Fig. 3 were used with different

![Collimator Diagram](image)

Fig. 10. Comparison of cardiac index values calculated from an arterial sampling curve and both right and left external heart curve calibrated at 5 minutes after injection.
focusing angulations against the chest wall. Comparisons of both the left and right precordial method calibrated at 5 minutes with the direct arterial method are illustrated in Fig. 10.

When the narrow collimator A with small inclination was used for the right external technique, the values obtained were too large since marked increase in external dilution values appeared. However, if the moderate collimator with adequate inclination was employed and a selective placement on the cardiac region was made, the obtained values were in reasonable agreement with those of the direct ones. When the left external technique was employed, where the collimator was focused over the cardiac apex, there was no difficulty in selection of the inclination of collimator and the values obtained by either collimator A or B well agreed with those of direct technique. The collimator C with minimal collimation in our series, though in only few cases, also gave satisfactory results. In cases with severe heart failure, it gave lower values as compared with direct technique.

From the above mentioned results, our standard technique for the external measurement of cardiac output was decided as follows: Collimator B is employed, which is focused over the cardiac apex with an inclination of 30 to 40 degrees against the horizontal plane and the calibration is made at 5 minutes after the injection.

3) Cardiac output in various diseases

The values of cardiac index determined by our method was 3.7 ± 0.3 L./min. in normal control, 1.8 ± 0.2 L./min. in heart failure, and

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![Fig. 11. Cardiac index determined by left precordial method calibrated at 5 minutes after injection.](image)

*Note:* These 2 cases were calibrated at 10 min.
4.5 ± 0.7 \text{L./min.} in liver cirrhosis. The values in hyperthyroidism or anemia were larger than normal control (Fig. 11).

4) Successive determination of cardiac output

One of the advantages of this radioisotope external method for the measurement of cardiac output is that several determinations can be performed repeatedly within a short time. When the successive determinations of cardiac output were carried out on the same subjects, relatively constant values were obtained with an average deviation between +5.8\% and −4.8\% and the maximal deviation within ±13\% (Fig. 12). Thus
the changes in cardiac output over ±13% were considered to be significant.

In a series of determination in 6 cases consisting of 3 normal subjects and 3 cases of heart failure, 250 mg. of aminophylline was injected intravenously, and the measurement of cardiac output was repeated 2 or 3 times within 15 to 25 minutes. Aminophylline produced little or no change in cardiac output in normal control but in patients with heart failure it caused an increase in cardiac output after about 10 minutes (Fig. 13). This increase was especially remarkable in cases whose cardiac output was low before the administration of the drug. As shown in Fig. 14, following the injection of aminophylline in cases of heart failure, the appearance time and the disappearance time gradually shortened and the slope of the final extrapolated curve became steep, resulting in a shortening of the circulation time and an increase in cardiac output.

**DISCUSSION**

For the calibration, the *in vivo* blood has to be drawn at the time when the external detector records the radioactivity of just identical mixing pool observed by the detector during the primary circulation curve. Calibration has been performed by many authors5–13) at 10 to 15 minutes after radioisotope injection when relative equilibrium has been reached.
According to MacIntyre and collaborators, if the counting rate at this time shows lower value than that immediately following the primary curve, it is considered that the calibration requirements are satisfied and that the observed pool had no later component that comes into the region after the period of primary circulation. However, the authors examined the variation of both in vivo blood and external dilution values successively and pointed out the fact that the conventional calibration time must be improved to obtain the cardiac output values which show better correlation with direct ones.

As indicated above, external cardiac output demonstrated higher value by conventional 10 minute calibration method than 3 to 5 minute ones in control cases, and the values calibrated at 5 minute after injection were in most reasonable agreement with those of direct method. The reason of this was also investigated, since a marked discrepancy between the decrease in external dilution value and that in blood dilution value was observed at 10 minutes. In other words, this is due to some smaller later component which comes into the region under the scintillation head, probably participation of some slower mixing phases, gradual increase in whole body background and so on. These slower mixing phases have been neglected or considered to be insignificant by other authors. In our opinion, the observed increase in external dilution value can be attributed mainly to the later appearance of radioactive isotope within the intervening tissue under the scintillation head. The lack of this increase in cases of heart failure can be explained by an assumption that the mixing process is still progressing in this period resulting in such a marked decrease in the dilution value that the increase due to the activity within the tissue is too small to manifest itself. However, as in control, marked discrepancy between these 2 dilution values appeared in cases of heart failure 15 to 30 minutes after the injection and supported validity of our assumption.

Thus the calibration should be made after the fairly complete mixing is reached but before the increase in external dilution value takes place. According to our data, 5 minute calibration seems to be most appropriate from this point of view, and the values calibrated at 5 minute were in best agreement with those obtained by direct method (Fig. 9).

As for the placement of scintillation head, the authors recommended the left cardiac apex monitoring with 5 minute calibration as the standard method. By this method, the difficulty to decide the suitable position and angulation could be minimized and the obtained values correlated well with those of direct ones. MacIntyre and associates informed that the left heart focusing method was recommended, because abnormally high cardiac output may be recorded by right heart focusing method owing to
possible poor mixing of the radioactive tracer. The advantages of the left precordial method over the right one were also pointed out in cases of heart failure or obesity, since these cases are frequently associated with left heart enlargement. Zipf and collaborators focused external detector on the middle of cardiac shadow, and Huff Schreiner and their associates upon the aortic arch with narrow collimation. In principle, external monitoring of head curve could be used for measuring cardiac output by the injection method, but Feer pointed out that it was not very successful because of the rather high standard deviation of the result (25%). Our findings confirmed and extended the observations of Huff, MacIntyre and their coworkers who found good correlations of flow rates when compared to measurement made by Fick and direct arterial Hamilton determination. In addition, simultaneous direct arterial and our external cardiac output determination showed no significant differences. These findings could be attributed to adequate placement, collimation of the detector and improved 5 minute calibration method.

The validity and applicability of this method is further supported by many authors. The difference between the values measured by external method and direct arterial method was within ±9% by MacIntyre and within ±10% by Feer. An average deviation of the external values from the Fick values was within 10% (Seldon) or +8.7% (Sharpe), and no systemic difference could be found by Schreiner between these 2 methods.

However, the principal disadvantage of this method is that the applicability of this method is sometimes limited in the presence of severe decompensated heart failure. As shown in Fig. 14, both the cardiac output and the slope of the dilution curve obtained by the direct technique were larger than those by the external technique. Under such circumstances the composite precordial curve seems to be particularly unreliable if one wants to obtain accurate absolute flow rate by this method. Relatively large values in direct technique are attributed to the fact that the calculation is based on the dilution curve of rapid circulating space. On the other hand, the dilution curve of external technique is a complicated one since it is influenced by many factors such as the increase in residual volume of the heart and transit of the isotope into the slow circulating space within the lung. In addition, the difficulty in separation of the recirculation wave and the delay in the clearance slope of the external dilution curve are thought to make the calculated values of cardiac output smaller. However, this method still has advantages if successive determinations are performed in such cases of heart failure as illustrated in Fig. 14.

We cannot overestimate the usefulness of a single determination of
cardiac output to distinguish border lines of cardiac disease, since existing standard of the cardiac output at resting state shows widely scattered ranges and many patients fall within the normal limits. The successive measurements of cardiac output by external monitoring may add another important clinical evaluation of cardiac function. Authors have explored the clinical applicability of a cardiac output test in response to aminophylline injection with external monitoring in this report. Zipf and collaborators performed serial cardiac output determinations in response to the load imposed by the Master test and Mahoney suggested the usefulness of this method to diagnose the prognosis of heart disease by measuring successively the changes of cardiac reserve, especially in cases of myocardial infarction. Thus this technique has the potential of providing important additional information on the dynamic pump function of the heart in response to drugs, exercise and postural change, and these informations may be of significant value in the clinical examination of cardiac function.

**SUMMARY AND CONCLUSION**

1. An improved apparatus for the external counting of the radioactive isotope was deviced, which enabled us to make a digital recording and printing with an increased accuracy, without a time delay and has special device to remove background counting rate automatically from the final reading. This apparatus was proved to be adequate for the exact external measurement of the cardiac output as well as for the successive determinations.

2. Several fundamental problems concerning the external measurements of cardiac output in man were investigated. The placement of the collimator focusing directly over the apex of the heart and the calibration at 5 minute were found to be most appropriate.

3. Taking these results into account, the cardiac output was determined by means of external technique in 37 cases including normal subjects and patients with heart failure, liver cirrhosis, anemia and hyperthyroidism.

4. The values obtained were in reasonable agreement with those of direct arterial sampling technique except in cases of severe heart failure.

5. Successive determinations of cardiac output were performed in 6 cases before and after the intravenous injection of aminophylline. The response to the drug was different between the normal subjects and the patients with heart failure.
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