The Determination of Cardiac Output by the Dilution Method without Arterial Sampling

I. Analytical Concepts

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The selection of an external site for a radioisotope determination of cardiac output is discussed with respect to satisfying the analytic conditions of the Stewart-Hamilton dilution equation. Examples of both single-chamber and multichamber recording are illustrated, along with a discussion of the difficulties of curve calibration and extrapolation from multiple sites. The development of a method independent of critical placement or patient variability is described.

Although earlier determinations of cardiac output in this laboratory by the radioisotope dilution method were performed by isolating the flow from a specific artery, such sampling is not required by the general formulation of the method. Since the obviating of the arterial puncture would considerably simplify this measurement clinically, studies have been extended to determine cardiac output by focusing a gamma ray detector externally over the region of the cardiac chambers or great vessels. We have been concerned since 1951 with the selection of a site that could be observed externally with sufficient reliability for this technic to be accepted as a routine clinical measurement. Many sites of arterial flow may be chosen for quantitation of a dilution curve of cardiac output; therefore, the problem has resolved to a selection of such sites and technics that will not be critically affected by variations in patients.

It is the object of the following investigation to examine the choice of the external site with respect to satisfying the conditions of the Stewart-Hamilton dilution equation. This study has included the relationship of the recorded curve of the counting rate to dilution quantities, the calibration of in vivo recording, and the problems of adequate extrapolation of the dilution curve.

Method and Calculation of Cardiac Output

The determination of cardiac output by the dilution method is based on the measurement of the varying concentration of the injected material as it passes through the heart. If a small volume of highly concentrated material is injected into the inflow tract, the average dilution of the material coming out of the heart will be a direct indication of the volume passing through the heart and causing this dilution. The measurement of the change of concentration during a definite interval thus permits the output to be expressed as volume of flow per unit time. The dilution curves obtained in the following investigation have been measured by the recording equipment described previously. Iodinated human serum (\textsuperscript{131}I) albumin was used as the injected material, and an external scintillation counter was focused at the site of interest. The selection of collimation has been a function of the site chosen and will be discussed, in reference to the anatomic placement, in an accompanying paper.

Since the same total injected material, \( I \), must come out of the heart as was injected into the inflow tract, this quantity of injected material must be equal to the product of the flow rate, \( F \), multiplied by the concentration of the tagged material, \( c \), in the blood, integrated over the entire
time of the primary circulation. This is represented by the equation

\[ I = \int_0^\infty F \, dt \]  

and if \( F \), the flow rate or cardiac output, is constant during the time of measurement

\[ F = \frac{I}{A} \quad \text{or} \quad F = \frac{I}{\int_0^\infty c \, dt} \]  

where \( A \) represents the integral of the primary dilution curve \( \int_0^\infty c \, dt \).

The calculation of the cardiac output by the dilution method is then dependent only on the recording and integration of the dilution curve with time. This recording, which is uncomplicated for an externally isolated peripheral artery or direct arterial sampling, does present additional problems when extended to viewing the concentration of radioactive material in the large central vessels or chambers.

**Relation of Counting Rate to Dilution**

The first problem involves the relationship of the concentration curve, as recorded in counts per minute, to a dilution of the injected radioactive material in terms of microcuries per milliliter. In the following investigation, this relationship was obtained by assaying a sample of venous blood in vitro and equating this blood concentration in microcuries per milliliter to the response in counts per minute of the detector to this same concentration in vivo at the selected site.

Even in measurements involving arterial puncture, calibration of the counting system has been accomplished by withdrawing a blood sample at a time sufficiently long after injection for the concentration to be considered as constant over the period of its measurement. The final concentration in microcuries per milliliter is then determined in vitro. The injected dose, \( I \), is equal to the product of the concentration \( c_t \), and the equivalent volume of dilution, \( V \). Equation 1 is thus reduced to

\[ F = \frac{c_t \cdot V \cdot A}{A} \]  

It should be emphasized that \( V_a \) is not necessarily the circulating blood volume as usually calculated by dilution methods, but is actually the volume of dilution of the injected material at the time when the sample was
withdrawn. If a 10 minute mixing time is observed before withdrawal, this volume would in most cases clinically approximate the blood volume.

The use of $V_d$ as a calibration factor is valid, however, regardless of when it is withdrawn or whether final complete mixing has or has not been reached. Since the first term of this equation is a ratio, it is seen that the specific activity at final dilution, $c_p$, may be expressed in terms of counts per minute and the dilution curve expressed with an ordinate of counts per minute. This formulation is not required when the arterial flow is externalized and led past the detector, since the response of the detector to a known concentration of radioactivity may be easily ascertained. For an in vivo measurement, however, the complex geometric system cannot be duplicated for calibration, and thus it is necessary that the response of this complex system to a known concentration of injected material be accurately determined. For example, Milnor et al. using the ear for measurement of cardiac output by the injection of T 1824 dye, calibrated their system by arterializing the ear pinna and focusing the detector on the same site for the primary curve as for the final dilution.

Since it is rarely possible to select a site that has no return flow, the usual solution for this calibration has been to maximize the ratio of volume of direct arterial flow to vein and capillary volume. It is thus necessary in all external counting technics that curves be recorded from sites into which there will be minimal additional flow after the primary flow has been recorded.

Calibration of Dilution Curve

The use of a calibration factor to relate counting rate to dilution may be valid only when the condition is imposed that the identical mixing pool be observed by the detector during the primary circulation curve, as is observed at the time of calibration. If the observed pool has some later component that comes into the region after the period of primary circulation, the calibration described will be falsely high and the counting rate ratio in equation 3 will not be accurate.

This formulation is not confined to radioisotope technics but occurs in all cases of in vivo measurements where the complex geometric system cannot be duplicated for calibration and where it is necessary that the response of this complex system to a known concentration of injected material be accurately determined. For example, Milnor et al. using the ear for measurement of cardiac output by the injection of T 1824 dye, calibrated their system by arterializing the ear pinna and focusing the detector on the same site for the primary curve as for the final dilution.

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This problem of calibration has been illustrated in the following dilution curves. Figures 1 and 2 show dilution curves obtained by a successful recording from a highly collimated scintillation counter, focused over the right heart and aortic arch respectively. A considerable number of such single-phase dilution curves were recorded from a posterior focusing on the aortic arch. These curves have shown no interference or later rise from other chambers, and have allowed the calculation of reasonable values of cardiac output.

Unsuccessful curves from over the aortic arch as well as from over the femoral artery are shown in figures 3 and 4. Although each primary curve is fairly well defined, the general upward inclination following the primary curve shows the presence of later components or post-primary influx. In each case the detector has recorded activity from a volume of venous return that is of sufficient magnitude to invalidate completely the calibration of the curve. These curves indicate that the final level was not obtained from the same geometric sampling volume as the primary circulation curve. This was the difficulty with the femoral artery curve, with its accompanying large venous return (fig. 4), and is a constant danger of any highly collimated technic in which such a small volume of the primary mixing pool is measured that any additional volume may account for a large percentage error.

This problem does not preclude the recording of successful dilution curves by use of high collimation. We have discarded this method only because the requirement of critical placement has been too extreme with patient variability to be successful for routine clinical application.

In the following studies it was considered that successful calibration was attained if no rise is seen in the record immediately following recirculation. If the record remains level or falls, it is improbable that an appreciable component of venous or capillary flow was measured. This standard is empirical, and actual verification rests on the correlation with cardiac outputs calculated from withdrawn samples. It has been our practice to maintain the counter focused continuously over the site during the active measurement. For calibration, the in vitro blood has been withdrawn at a time sufficiently long after injection (10 to 15 minutes) that relative equilibrium has been reached. If the counting rate at this time of withdrawal levels off at a value less than the counting rate immediately following the primary curve, calibration requirements are considered as having been satisfied.

**Analysis of Multichamber Technics**

For a greater ratio of the volume of direct arterial flow to vein and capillary volume, a wider collimation has been utilized with placement closer to the chest wall. Since such wider collimation and focusing results in recording from multiple dilution sites, attention must be given to the extension of the gen-
GERAL CARDIAC OUTPUT FORMULA TO MORE THAN ONE CHAMBER.

IF 2 RECORDERS ARE RECORDING THE COUNTING RATE INDIVIDUALLY FROM THE RIGHT AND LEFT CHAMBERS OF THE HEART, EQUATION 3 WILL GIVE

\[ F_A r = c_r V_d \]  \hspace{1cm} (4)

\[ F_A l = c_l V_d \]  \hspace{1cm} (5)

IN THIS CASE \( A_r, c_r \) REFERS TO THE DILUTION CURVE AREAS AND FINAL CONCENTRATION OF THE RIGHT HEART ALONE WITH SIMILAR NOMENCLATURE FOR THE LEFT HEART. SINCE THE SAME FLOW, \( F \), GOES THROUGH BOTH SIDES OF THE HEART, THE SUM OF THESE 2 EQUATIONS, OR OF ANY NUMBER OF FLOW SITES, MAY BE CONSOLIDATED TO GIVE THE GENERAL EQUATION:

\[ F = \frac{c_r + c_l + \ldots + c_n V}{A_r + A_l + \ldots + A_n} \]  \hspace{1cm} (6)

EQUATION 6 STATES THAT IF A DILUTION CURVE IS RECORDED FROM A SOURCE OF 2 OR MORE SITES, THE OUTPUT MAY BE CALCULATED BY MEASURING THE AREA OF THE TOTAL DILUTION CURVE, PROVIDED THE CALIBRATION LINE IS OBTAINED WITH THE IDENTICAL GEOMETRIC RELATIONSHIP TO THESE SAME SITES. THIS HAS BEEN STATED IN A SLIGHTLY DIFFERENT WAY BY VEALL ET AL.6


PROBLEMS OF EXTRAPOLATION

IN EVALUATING THE COMPLETE CURVE OF PRIMARY DILUTION, EXPONENTIAL CLEARANCE HAS BEEN GENERALLY ASSUMED.14 WHILE DOW15 AND OTHERS HAVE POINTED OUT THAT THIS MAY NOT BE ENTIRELY VALID, IT IS STILL SUFFICIENTLY ACCURATE FOR CLINICAL DETERMINATIONS AND IS GENERALLY USED FOR QUANTITATION OF CARDIAC OUTPUT BY THE DILUTION METHOD. THIS ASSUMPTION IS VALID, HOWEVER, ONLY FOR PURE ARTERIAL FLOW OCCURRING IN A SINGLE TIME RELATIONSHIP. FOR THIS REASON, THE EARLY PART OF THIS INVESTIGATION WAS CONCERNED WITH THE ATTEMPTED ISOLATION OF ONE OR THE OTHER PRIMARY CHAMBERS. SUCH ISOLATION AVOIDED THE COMPLICATION OF EXTRAPOLATING THE DESCENDING DILUTION CURVE WHEN IT HAD A MULTICHAMBER TIME-PHASE RELATIONSHIP. ALTHOUGH
the assumption of an exponential clearance of the large chambers of the heart has been in reasonable agreement with observations, the summation of 2 or more time-phase curves is not exponential and can cause considerable departure from a semilogarithmic straight line.

This departure is illustrated in figure 6, which was obtained by a counter focused directly over the mid-precordium. The descending line in this case can be resolved into 2 components: one ascribed to the right heart and one ascribed to the left heart. The disadvantage of this type of curve is the difficulty in obtaining sufficient points to predict with reasonable accuracy the latter extrapolation. Since the extrapolated area is commonly 20 to 40 per cent of the total area, a few seconds’ variation in clearance time may cause the calculation of output to be considerably in error. It has been necessary, therefore, to avoid any precordial site that would exhibit roughly equivalent contributions from the 2 chambers.

Our approach has been to select preferentially either one dominant chamber or the other so as to obtain a reasonably long period of single-phase extrapolation. In figure 7, a predominant left heart focusing is shown and in figure 8 a predominantly right heart curve is illustrated. In both cases the line of extrapolation is sufficiently long for accurate prediction. Thus, 2 criteria have been followed in this work. The first is to maximize a single-chamber clearance so as to keep the extrapolated area at a minimum and the second is to obtain as many points on the descending portion of the final dilution curve as possible. If these conditions are observed, the choice of placement is secondary and may be made to fit the specific geometric configuration at hand.

**Discussion**

Since the formulation of the Stewart-Hamilton equation for the calculation of cardiac output is general, it is not surprising that successful output measurements may be obtained by the external focusing of a detector over many dilution sites after the injection of a radioactive material into the circulating blood. This investigation has shown only a few of the possible sites.
Of more importance, however, in the extension of these measurements to external technics is the observance of the 2 necessary conditions of this formula. The first is accurate calibration of the dilution curve and the second is the reasonable assumption of exponential clearance from the extrapolation of the dilution curve. It has been the purpose of this report to point out the difficulties of curve calibration with highly collimated counters and the problem of successful extrapolation when multichamber technics are employed.

Since the cardiac configuration is extremely variable from patient to patient, successful clinical application of this technic must not depend upon critical placement. If the site of placement is not constant, highly collimated technics may be difficult, and multichamber recording must be considered. It has been demonstrated that this latter may be most successful if 2 criteria are followed. The first is adequate extrapolation of the curve from the final clearing chambers. This is most easily obtained by accentuation of the radioactivity arising from the chambers of one side of the heart so that the contribution of the other chambers will not appreciably distort its final extrapolation. Secondly, because of the inherent uncertainty of the character of the extrapolated line, it is desirable to make the measured area as large as possible, so that errors arising from the extrapolated area will be at a minimum. If these conditions are observed, the choice of placement is secondary and may be made to fit the specific geometric configuration at hand.

**Summary**

The extension of the measurement of cardiac output by external detection of iodinated (I$^{131}$) human serum albumin has been described. The problems of calculating a single-chamber dilution curve are discussed and the technic of obtaining successful extrapolation of multichamber dilution curves has been considered.

Independence of placement with these technics is emphasized and examples are shown of similar outputs obtained at completely differing focusing angles.

**Summario in Interlingua**

Es describite le extension del mesuration del rendimento cardiac per le detection externa de albumina iodate (I$^{131}$) in le siero human. Es discutite le problemas de calcular curvas de dilution a camera unic. Es etiam prostate attention al technica de obtenre un valide extrapolation de curvas de dilution a plure cameras.

Es sublineate le independentia del placement in le uso de iste tecnica. Exemplos es presentate de simile valores de rendimento cardiac obtenite per medio de completely differente angulos focal.

**References**


Medical Eponyms

By Robert W. Buck, M.D.

Ayerza’s Disease. This symptom complex was first described by F. C. Arrillaga of Buenos Aires, a former pupil of Professor Abel Ayerza at the Hospital de Clinicas in that city, in an article entitled “Sclerosis of the Pulmonary Artery Secondary to Certain Chronic Pulmonary Conditions (Black Cardiaes)” (Scélerose de l’artère pulmonaire secondaire à certains états pulmonaires chroniques (cardiaques noire), which appeared in the Archives des Maladies du Coeur des Vaisseaux et du Sang 6: 518-529, 1913.

“On August 20, 1901, Professor Ayerza (of Buenos Aires) demonstrated a patient in whom a peculiar form of cardiac insufficiency had drawn his attention. Struck by the color of this patient, he had called him a black cardiac. The pathological anatomy of these forms of illness never having been described, the present study will attempt to fill this gap, by presenting the complete picture of the disease as it appeared in eleven cases together with radiographic pictures . . . It nearly always affects subjects who have not yet passed their fifties . . . They have chronic disease of the respiratory tract going back ten, twenty, or even twenty-five years . . . they are emphysematous. It is this condition which eventually secondarily involves the pulmonary artery, causing it to become sclerotic, and the heart, leading to its hypertrophy . . . The sign which first attracts one’s notice in examining the patient is the cyanosis.”
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