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Use of radioiodinated human serum albumin and external body counting in the determination of cardiac output in human subjects

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THE USE OF RADIOIODINATED HUMAN SERUM ALBUMIN AND EXTERNAL BODY COUNTING IN THE DETERMINATION OF CARDIAC OUTPUT IN HUMAN SUBJECTS.

by

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I. PREFACE

The work reported in this paper is a continuation of a course of study undertaken during the academic year 1959-1960, at the Radioisotope Service, Omaha Veterans Hospital, the report of which was submitted to Creighton University as a Master's thesis. The earlier paper, which contains a fuller consideration of background material than is presented here, is available either through the Radioisotope Service at Veterans Hospital or the Graduate School of Creighton University.

The study and experimentation which constituted the subject matter of the earlier paper had been elaborated *in vitro* and in animals; the current thesis details further developments in theory and technology, and a report of a series of some ninety determinations made on human subjects.

II. DETERMINATION OF CARDIAC OUTPUT BY THE USE OF RADIOISOTOPES AND EXTERNAL BODY COUNTING

The chief advantage in estimating cardiac output by the use of radioisotopes with external counting over the precordium lies, in our opinion, in the simplicity of the patient's role in the performance of the procedure. Estimation of cardiac output by the Fick gas principle or the dye dilution principle involves variously cardiac catheterization, arterial puncture, and/or a certain amount of intelligent cooperation on the part of the patient. While these are not insurmountable obstacles, they must be weighed against the value of the information to be obtained, and tend to limit the applicability and usefulness of the procedure. In the radioisotope technic with external counting, the patient is subjected only to

two peripheral venipunctures spaced six-ten minutes apart; his cooperation is required only to the extent of lying quietly on the table for a similar period of time.

The work reported in this paper was directed chiefly at the introduction into the procedure of technical refinements which should add both to the accuracy of the method, and to the simplicity of its performance.

Hopefully, not the least significant portion of this paper is that which deals with the introduction of modern electronic data processing into the mechanics of the mathematical computation. As will be seen, the mathematics involved, while not abstruse, are at least complicated; their calculation is laborious and time-consuming. Recently, the Radioisotope Service at the Veterans Hospital had acquired an IBM 1620 computer; the first phase of the current project consisted of programming

the mathematics of the procedure into the language of the computer. The utilization of electronic computing has made the performance of the procedure a much briefer and more systematic task.

A word about the practical steps in the performance of the procedure is in order: the patient, first of all, is positioned supine on an ordinary examining or other table. Then an external scintillation detector is positioned over the chest, so that some large volume of blood is within the field of sensitivity of the counter. The precise position of the external detector is not highly critical, as long as during any one determination the same position is maintained. A preliminary background count is recorded. The proper adjustments having been made on the recording equipment, injection

of 7-20 microcuries of RISA [1] in 0.5 to 1.5 ml. saline solution is made rapidly into a large peripheral vein. Pertinent counts and times are recorded. Some minutes later (five to eight), when the isotope has had time to become thoroughly mixed in the blood, and with the patient and the scintillation detector in the same position, an external count rate is recorded; simultaneously, blood is withdrawn from a peripheral vein. The values obtained at this time are used for calibration purposes. This terminates the patient's part in the procedure, about ten minutes having elapsed from beginning to end of the test.

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(1) RISA - (ABBOTT) is Human Albumin, tagged with I-131. This large molecule is used so as to keep as much as possible of the injected indicator within the vascular bed during the actual time of the procedure.

III. MATHEMATICAL THEORY OF THE PROCEDURE

The approach taken here differs slightly from that usually employed. Emphasis is placed in this presentation on the significance of the total external count registered during the first passage of the isotope under the external detector as containing within it quantitative relationships which permit the calculation of cardiac output.

It is the feeling of this investigator that within the boundaries defined by the nature of the procedure, the primary information available is reported by the scaler, which tallies directly the count registered by the external detector. On a theoretical basis, the more directly this information can be used, and the less one has to rely on intermediate steps such as the drawing of a graph by some sort of count-rate estimator, and the personal interpretation of that graph, the more accurate the over-all procedure should be.

When a radioactive, or for that matter, colorimetric indicator is injected into a peripheral vein, it is carried in the bloodstream to the heart, is pumped through the pulmonary circulation, and eventually out into the systemic circulation. The indicator is carried in a discrete volume of blood; its concentration in this finite volume by the time it reaches the systemic arterial system is not constant, but tends, if one particular point is chosen as an "observation station" from which to view the changing concentration as the indicator-containing blood is swept by, to increase from zero, then to plateau somewhat, and finally to decrease again towards zero. Unfortunately, as far as calculating cardiac output is concerned, the concentration, when observed as described, never reaches zero value due to recirculation of blood containing indicator from near parts of the body. This recirculation tends to obscure

the tail of the concentration-decline curve; however, theoretically and empirically, the decline is found to fit closely the characteristics of an exponential function. If it is assumed that in all cases the decline will be nearly exponential, one can make an extrapolation to zero concentration which will not deviate too much from the actual values that would be observed, did not the recirculation phenomenon occur.(2)

Generally, then, theory states that if the amount of indicator injected is known, and if both its average concentration in the carrying volume, and the time of passage of this volume can be determined, flow (or cardiac output) can be estimated by a simple extension of the familiar

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(2) Discussion of this principle can be found in many places in the literature. Cf the article by W.F. Hamilton, et.al., in Am. J. Physiol. 153:309, 1948: "Comparison of the Fick & Dye Injection Methods of Measuring the Cardiac Output in Man." Titles of several other pertinent articles are included in the bibliography at the end of this thesis.

dilution principle of volume determination, according to the equation:

$$\text{Flow} = \frac{\text{indicator injected}}{\text{average concentration x time}} \qquad (1)$$

The changing concentration, as well as the time of passage, can be determined by serial arterial sampling, whether the indicator used be a radioactive or colorimetrically measurable substance.

In the context of the radioisotopic method with external body counting, the detector, positioned over the precordium, ignoring for a moment the recirculation phenomenon mentioned above, would record a given number of counts due to the first passage of isotope through and out of the heart into the systemic arterial circulation, and would do so in a definite period of time. It can be intuitively seen that the magnitude of the total recorded count will be directly proportional both to the concentration of isotope in the volume of blood "seen" by the detector, and to the time it

takes for the carrying volume to pass beneath it: the more isotope there is per unit volume of blood seen, the higher will be the count; similarly, the longer blood containing isotope remains beneath the detector, the higher the count again will be:

$$Ct \propto C,T, \tag{2}$$

where Ct = total count, C = concentration of isotope in the bloodstream, and T = the time of first passage of blood containing isotope beneath the detector. Since the total activity seen by the detector, and hence the total count recorded, depends precisely on the duration of time a given concentration is "seen", generally it can be stated:

$$Ct \propto C \times T \tag{3}$$

As pointed out, the concentration is not constant, but varies. Therefore, a more precise formulation states:

$$Ct \propto \int_0^\infty \bar{C}(t)\,dt \tag{4}$$

where C(t) is used instead of C, since C is found to vary with time, and where the entire right hand side of the expression signifies the integration with respect to time of all instantaneous concentrations of isotope during the first passage of the carrying volume.

A factor of proportionality must then be found to convert the expression to an equation. Under the specific circumstances of a given output determination, the time is determined by the dynamics of flow, and so becomes specified. Variability, however, is to be found in the sensitivity of the detecting apparatus to the concentration of isotope in the carrying volume. This variability depends on the precise (and, incidentally, non-discoverable) geometry of the volume seen, on the thickness of the patient's chest wall, the inherent characteristics of the equipment used, and similar factors. In order to

quantify the sensitivity of the detecting system to concentration, a count rate with the scintillation detector in position over the chest is taken after the isotope has become thoroughly mixed in the blood; simultaneously, blood (which contains, presumably, the same concentration of isotope as is in the blood seen by the detector) is removed via peripheral venipuncture.

If an accurately measured aliquot of drawn blood is then counted in such an instrument as a well scintillation crystal, the concentration of isotope in the blood can be determined in terms of counts per minute per ml (CPM/ml). The ratio, then, of the external count rate taken at the time of withdrawal of blood to the concentration of isotope in the drawn blood expressed as mentioned is the factor of proportionality which converts expression (4) into an equation:

$$Ct = \frac{CPM_e}{CPM/ml_b} \times \int_0^\infty C(t)\ dt \qquad (5)$$

But, over a short period of time, the instantaneous concentration of isotope multiplied by the amount of blood that leaves the heart during that interval is equal to the amount of isotope leaving the heart during the same time, or:

$$F_{\Delta t} \times C_{\Delta t} = I \qquad (6)$$

where $F_{\Delta t}$ = flow of blood during the time interval, $C_{\Delta t}$ = concentration during interval, and I = amount of isotope leaving the heart during the interval.

Extending the same principle throughout the entire time of the first passage of the isotope, the total amount of the isotope injected is equal to the concentration of isotope integrated with respect to time, multiplied by the cardiac output, or: $I = F\int_0^\infty C(t)\ dt \qquad (7)$

where I is now equal to the total amount of isotope injected. Transposing: $F = \frac{I}{\int_0^\infty C(t)\ dt} \qquad (8)$

And, transposing equation (5):

$$C(t)\ dt = Ct \times \frac{CPM/ml_b}{CPM_e} \qquad (9)$$

Substituting into equation (6):

$$F = \frac{I}{Ct \times \frac{CPM/ml_b}{CPM_e}} \qquad (10)$$

Variables whose values can be empirically found are seen now to occupy the right hand side of the equation. It need be noted that the isotope injected (I) must be expressed in terms of CPM as determined under the same conditions used to measure the concentration of isotope in the drawn blood, in order to preserve dimensional comparability.

To this point has been demonstrated the general mathematical validity of calculating the cardiac output primarily as a function of the total count registered over the precordium as a result of the first passage of isotope under the detector; the problem of the recirculation phenomenon has not

been dealt with. In actuality, a total count cannot be directly recorded, for reasons mentioned. To overcome this difficulty, we have introduced the following additions of apparatus and technic into the system: two scalers are used instead of one. Of these, one tabulates directly from the detector; the second scaler operates in dependence on the first. Whatever counts over a given period of time are tallied by scaler #1 are also tallied by scaler #2, provided it is at that time in operation. It does not tabulate at all unless scaler #1 is in operation, and can be switched on and off without disturbing scaler #1. With this arrangement, the detector and scaler #1 can be turned on any time prior to the injection of indicator, and be permitted to scale counts and drive the graphing mechanism throughout the critical time of the procedure; no numerical

count is taken directly from scaler #1 at the time of the passage of injected isotope for the first time beneath the detector. At the moment of injection, scaler #2 is switched on and allowed to tabulate the count which scaler #1 is picking up from the detector. After the count rate begins to decrease, but before the effect of recirculation appears, scaler #2 is manually stopped, while #1 continues tabulating counts and driving the grapher. Thus the second scaler records the count caused by the first passage of isotope up to a somewhat arbitrary point on the downswing of the count-rate curve. Scaler #1 is permitted to continue recording, both to make certain that #2 was in actuality stopped on a well-established curve, and also to have produced as many points as possible from which to calculate the mathematical slope of the downswing.

As has been explained, the decline in concentration of isotope and hence in count rate is nearly exponential; the points taken, then, from the grapher, when transferred to semi-log paper determine a straight line, the area under which can be calculated by the equation:

$$A = \frac{Y_o}{m} (e^{mt} - 1) \qquad (11)$$

where Y_o = count rate at the time of the picture, m = slope of the line, and t = the time required for the extrapolation curve to reach a count rate equivalent to zero concentration of isotope in the volume of blood seen by the detector.

The slope of the line is calculated by the formula:

$$m = \frac{\ln (Y_t/Y_o)}{t} \qquad (12)$$

where other symbols are as above, Y_t = the predetermined background level. (It should be noted that we have usually had no significant

difficulty in stopping scaler #2 at a suitable place on the downslope of the curve.) The area calculated is in the mathematical dimension of CPM x time, which can be seen to be equivalent to an absolute number of counts:

Counts/minute x time = counts (13)

This value when added to the counts from scaler #2 gives the number of counts which would result from the first passage of isotope did recirculation not occur. The proper dimensions, of course, have to be preserved.(3)

At the time of writing of this paper, the procedure as now in use is as described. Also, a method of mathematical calculation has been in part worked out and programmed on the computer, which should eliminate completely the element of human judgment in deciding where the extrapolation should

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(3) Cf pertinent sections in the chapter on the computer program for a more particular explanation of individual steps in the general mathematical theory here proposed.

begin. Equipment is only now being made available which reports data in the form required by this development. It is hoped that in the future this new approach may be practically implemented.

The object of the alterations made so far in the procedure as usually performed, and of the developments not yet brought to fruition is to remove from the technic the necessity of measuring the physical area under a graphed line, which, since it is not a straight-line function on Cartesian coordinates, must be done by the use of a planimeter, by weighing the paper area after it has been cut out, or similar procedure. Not only does our approach simplify the performance of the procedure, but it should theoretically contain less chance of error, considering the fact that at best a mechanically drawn graph implies an interpretation of primary data, which could be as accurate as, or more accurate than, the primary data only fortuitously.

There are certain matters pertaining to scale factors, radioactive background, etc., which have not been fully discussed in the presentation so far. It was thought best to treat these matters in the section on the computer program, since their handling falls naturally into that context.

IV. INSTRUMENTATION

This chapter describes briefly the actual instrumentation used in the current series of experiments. It should be pointed out, however, that this equipment is not highly specialized, and suitable instruments which may be adapted to the technic should be available to the average well-equipped radioisotope installation.

Generally, there are two types of radioactive measurement to be made in the procedure: 1) external body counts, and 2) counts of accurately measured fluid aliquots in a well type scintillation crystal counter system. The latter system consists of a heavily shielded scintillation crystal, enveloped in a light metal can, into the top of which a cylindrical port has been made for the reception of a small test-tube containing the material to be counted;

of a photo-multiplier tube which converts the scintillations caused by radioactive emanations in the crystal into transmittable electrical impulses; and of a scaler, which tallies the impulses so transmitted. This is more or less standard equipment for medical work with radioactivity; in the cardiac output technic it is utilized for quantification of the radioactive content of 1) a dilution of the injected material, 2) blood drawn by venipuncture prior to the running of the procedure, provided the patient has recently received isotopes, and 3) blood drawn by venipuncture after the radioactive indicator has become thoroughly mixed in the patient's circulation.

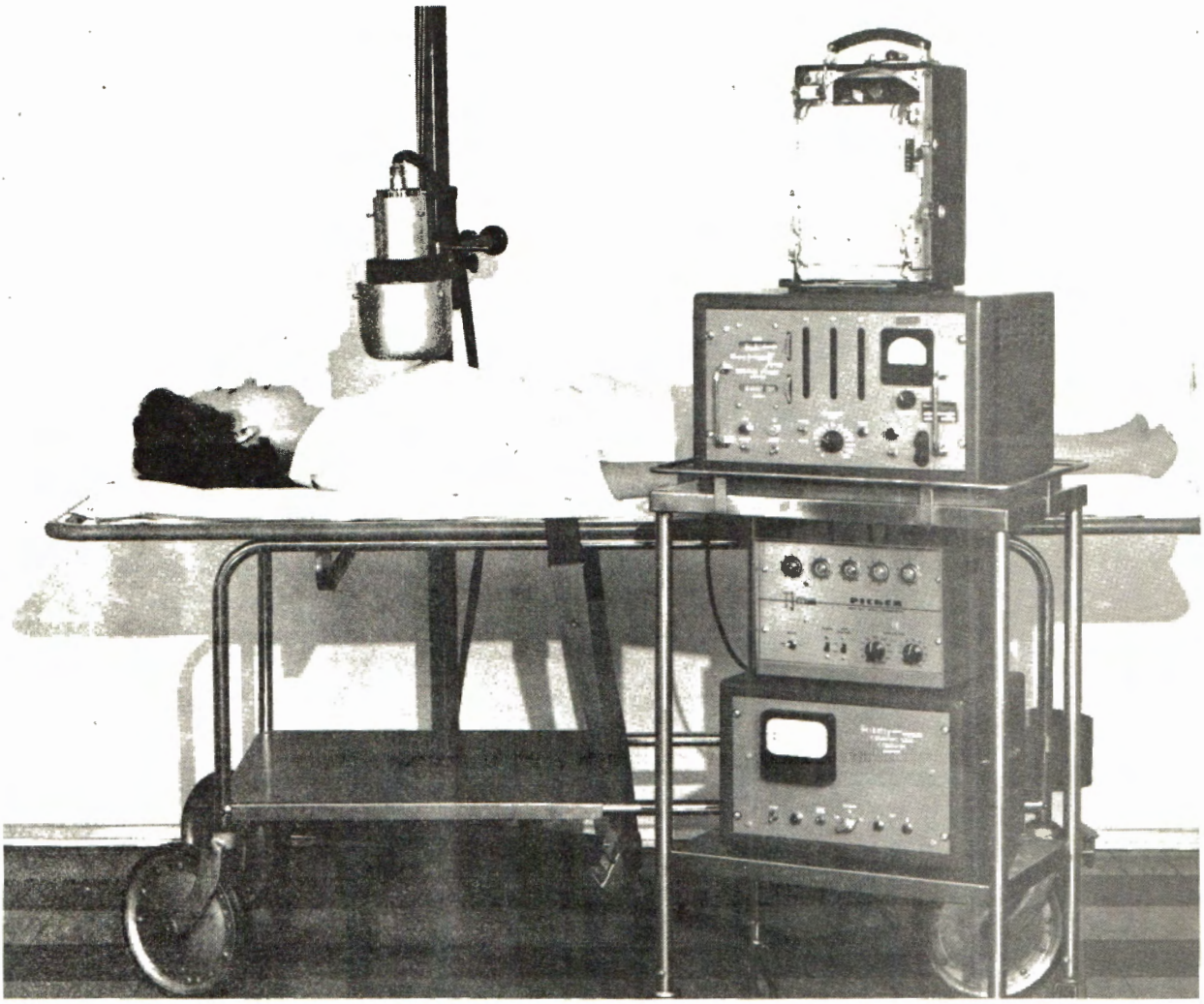
The external body counting system consists of a boom-supported, movable, heavily shielded scintillation crystal and its photomultiplier tube, two scaling units, a count rate computer, and a grapher which creates a permanent record of the changing count rate.

The external counting instrumentation used in the current study is pictured on page 24.

1. The scintillation counter and photo multiplier tube. In our set-up, this is a Berkeley Model 2770 Detector, encased in a modified shield and collimator, which provides excellent cut-off of side-incident rays and a fairly broad cone of sensitivity.

2. The Primary Scaler. This is a Berkeley Model 2001 Scaler, whose design is immediately compatible with the 2770 Detector. It is set up for pre-determined count cut-off or impulse transferral. In the cardiac output procedure, it is used in the latter mode to drive

3. The Count-Rate Computer. This also is compatible equipment, a Berkeley Model 1600 Counting Rate Computer. This operates to provide a meter reading of count rate integrated over the time interval of the pre-determined count cycle, information which is transmitted from the primary scaler.



DETECTION AND RECORDING EQUIPMENT

Over Patient:

Berkeley Model 2770 Detector

From Above, on Cart:

1. Esterline-Angus Graphing Ammeter
2. Primary Scaler. Berkeley Model 2001.
3. Secondary Scaler. Picker Model 5810.
4. Berkeley Model 1600 Counting Rate Computer.

4. The Esterline-Angus Graphing Ammeter. This machine is a model capable of being incorporated into many different systems, is made by a different manufacturer, and is not specific to the instrumentation so far described. It is however, compatible with the output of the Count Rate Computer. The graph that it draws indicates time on the abscissa and count rate on the ordinate. It is from the downswing of the curve caused by the changing count rate recorded over the precordium that the extrapolated count is calculated in the cardiac output procedure.

5. The Secondary Scaler. The exact model to be used is inconsequential to the procedure, as this phase of the instrumentation serves only as slave counter to the primary scaler during the time from the injection of indicator to the beginning of the extrapolation.

In our set-up, we have utilized a Picker Model 5810 Scaler, which is a transistorized and relatively inexpensive machine made primarily for instructional purposes. The necessary adaptations having been made, it is capable of being started or stopped by independent hand switches on lengths of electric cord. This arrangement has proved to be quite workable in practice.

V. THE IBM PROGRAM

The IBM 1620 electronic computer is a recently developed instrument, specifically designed for the processing of scientific and technical data. Transistorized circuitry and a high degree of internal flexibility enable the instrument to perform computation heretofore requiring much larger and more expensive installations.

Internally, the system operates entirely in terms of decimal digits. There is a digital machine language in terms of which all operations are performed. Any program is ultimately expressed in terms of this machine language, so that it may be handled by the computer. In order, however, to overcome the tediousness and complexity involved in constructing and expressing a program in terms of machine language, which would be an extremely involved procedure if the program under

consideration were at all complicated, there have been developed systems, or programs, whose sole purpose is to convert into machine language statements and relations expressed in a manner that is quite similar to familiar modes of expression.

Such a translating system is Fortran (FORmula TRANslation), utilized in the preparation of the program currently under discussion. This system is so worked out as to enable the programmer to express his material for the most part in the form of mathematical equations. When the computer then, has been loaded with the Fortran Processor Program, it is capable of translating the data fed to it in terms of mathematical statements into its own internal language. One statement, accordingly, expressed in Fortran language, is capable of generating a multitude of statements in machine language. As would be expected, for the machine to be able to perform such translation, rigid

rules must be followed in the formulation of expressions, but, with a little practice, one rapidly becomes familiar with the possiblities and restrictions of the system.

The cardiac output program, as currently in use, follows the logical structure of the mathematics explained in the previous section; to this, however, is added a larger structure designed to provide ease and continuity in the actual process of caluculation. The final program, translated into machine language, is punched out by the machine onto paper tape. When it is desired to calculate an individual determination, or series of determinations, this paper tape is fed into the computer, thereby impressing on the machine's memory the logic it requires for the solution of a problem. With a tap on the "START" button, the machine verbally asks, via the typewriter, for the

different variables required for computation. It then holds itself in readiness for the reception of data, also to be entered from the typewriter. When all the variables have been entered into the computer, the machine calculates the answers; this it does with great rapidity; its results are then typed out on the typewriter. Thus not only is the computation performed, but a permanent record of the results of computation is also produced.

An actual print-out from the computer of the cardiac output program follows; the format is that of Fortran statements. The statement numbers in the far right-hand column are not a part of the program; they have been added for the purpose of reference in the present discussion.

```
DUM = 13Ø.                                                    1
DX = 1ØØØ.                                                    2
DO 1 I=1,9                                                    3
DUM = DUM+DX                                                  4
1 D = SAY(DUM)                                                5
2 PAUSE                                                       6
D = SAY(-11Ø1.)                                               7
ACCEPT, WPD, HIN, AMT                                         8
D = SAY(-21Ø1.)                                               9
ACCEPT, BGE, FAC, CDR, TDR, CTE                              10
D = SAY(-31Ø1.)                                              11
ACCEPT, YO, YT, T                                            12
D = SAY(-41Ø1.)                                              13
ACCEPT, BGW, BBG, CBL, CDL, DIL                              14
WKG = WPD*Ø.45359                                            15
HCM = HIN*2.54                                               16
A = (WKG**Ø.425)*(HCM**Ø.725)*Ø.ØØ7184                       17
DRC = CDR-(BGE*TDR)                                          18
SLP = (LOG(YT/YO))/T                                         19
XTR = (YO/SLP)*(EXP(T*SLP)-1.)                               20
XTRCT = (XTR-(T*YT))*(FAC/6Ø.)                               21
CTOT = DRC+XTRCT                                             22
CTI = ((CDL-BGW)*DIL)*(AMT)                                  23
CAL = (CBL-BBG)/ (CTE-BGE)                                   24
F = CTI/(CTOT*CAL)                                           25
FIL = F/1ØØØ.                                                26
CI = FIL/A                                                   27
D = SAY(-51Ø1.)                                              28
PRINT, CTI                                                   29
D = SAY(-61Ø1.)                                              30
PRINT, DRC, XTRCT, CTOT                                      31
D = SAY(-71Ø1.)                                              32
PRINT, CAL                                                   33
D = SAY(-81Ø1.)                                              34
PRINT, A                                                     35
D = SAY(-91Ø1.)                                              36
PRINT, F, CI                                                 37
GO TO 2                                                      38
END                                                          39

LOAD WPD, HIN, AMT.                                          40
LOAD BGE, FAC, CDR, TDR, CTE.                                41
LOAD YO, YT, T.                                              42
LOAD BGW, BBG, CBL, CDL, DIL.                                43
NET INJECTED COUNTS=                                         44
NET DIRECT, EXTRAPOLATED, TOTAL COUNTS=                      45
CALIBRATION FACTOR=                                          46
SURFACE AREA IN SQUARE METERS=                               47
CARDIAC OUTPUT, CARDIAC INDEX=                               48
```

The symbols assigned to the variables used in the program are explained as follows:

WPD = weight of patient in pounds.

HIN = height of patient in inches.

AMT = amount in ml. of RISA solution injected.

BGE = background, external; i.e., background in CPM as measured by the external recording apparatus with the detector in position over the chest of the patient.

FAC = a scale factor set on the count-rate computer prior to the recording of the concentration curve.

CDR = count, direct; i.e., the gross count recorded up to the point on the curve which is established at the beginning of the extrapolation.

TDR = time, direct; i.e., the time in decimal minutes from the beginning of the recording of the concentration curve

to the point which serves as the beginning of the extrapolation. This is the time it has taken to accumulate CDR.

CTE = count, external; i.e., the count rate in CPM recorded by the external detector after the isotope has become mixed in the bloodstream.

YO = the value of the instantaneous count rate at the beginning of the extrapolation, read from the graph drawn by the count-rate computer-grapher combination.

YT = the value of the instantaneous count rate at the end of extrapolation. This value is obtained by dividing the radioactive background by the scale factor used on the count-rate computer (BGE ÷ FAC).

T = the time required to complete the extrapolation, obtained from the graph of the extrapolation drawn on semi-log paper; expressed in decimal seconds.

BGW = background, well; i.e., the air background in CPM recorded by the well scintillation crystal in which both the dilution of the injection material and the blood drawn after mixing from the patient are counted.

BBG = blood background; i.e., the count level in CPM/ml of blood drawn from the patient prior to the performance of the procedure, as measured in the well scintillator, if the patient has recently received diagnostic or therapeutic radioactive material. If such is not the case, the value of BGW is repeated in place of BBG.

CBL = count, blood; i.e., the count rate in CPM/ml of blood drawn from the patient after the isotope has become thoroughly mixed; counted in the well counter.

CDL = count, dilution; i.e., the count rate in CPM/ml of a dilution of the injection material; counted in the well scintillator.

DIL = dilution; i.e., the factor of dilution used in the preparation of an aliquot of injection material; counted in the well scintillator.

WKG = weight of the patient in kilograms.

HCM = height of the patient in centimeters.

A = area; i.e., the body surface area of the patient in square meters.

DRC = direct count; i.e., the net value of the count to extrapolation; equal to CDR less the appropriate background.

SLP = the mathematical slope of the line used in extrapolation.

XTR = the gross extrapolated area, calculated in CPM x seconds.

XTRCT = extrapolated count; i.e., the net value of an absolute count equivalent to the value of the graphed area; equal to the graphed area corrected to proper mathematical dimensions less appropriate background.

CTOT = count, total; i.e., the sum of net direct and extrapolated counts.

CTI = count, injection; i.e., the amount of radioactivity injected in CPM.

CAL = calibration; i.e., the mathematical expression of the sensitivity of the external detector to the concentration of radioisotope in the bloodstream.

F = flow; i.e., the cardiac output in ml/min.

FIL = flow in liters; i.e., equal to F/1000; used for calculating cardiac index.

CI = cardiac index; i.e., cardiac output expressed in terms of L/min/M^2.

In order to get the machine to use verbal statements, it is, of course, necessary to include these in the program. The verbal statements included in this program are numbered 40-48, and are handled by what is called the "SAY' sub-routine. Statements 1-5 prepare the computer to receive the nine statements used. Statement 6, "PAUSE", is included at the beginning of the actual operational portion of the program to enable the operator to set the paper in the typewriter, etc., according to his desires. A push of the "START" button when the computer has reached this point in the program causes the machine to proceed to the statements which follow.

Statements 7-14 cause the machine alternately to ask for and to receive into memory the variables required for calculation. Statement 15 converts weight in pounds to weight in kilograms; statement 16, height in inches to height in centimeters. (Chart records at OVAH show these values in English units; expression of cardiac output and cardiac index is desired in metric units, necessitating this conversion.)

Statement 17 calculates by empirical equation the body surface area of the patient in square meters, to be used in the calculation of the cardiac index.

Statement 18 converts the gross count to the beginning of extrapolation to a net value. The background in CPM recorded by the external detector prior to the recording of the counts from injection is multiplied by the time in decimal minutes required for the accumulation of the count to the beginning of the extrapolation; the product of these values is subtracted from the gross count.

Statement 19 calculates the slope of the line of extrapolation according to the formula given in the preceding section.

Statement 20 calculates the gross extrapolated area in the dimension of CPM x seconds.

Statement 21 both subtracts the appropriate background from the area calculated in statement 20, and converts the resultant value into the correct dimension; i.e., absolute counts. Multiplication by FAC is performed because the count rate signified by the line drawn by the grapher is smaller than the actual count rate by the factor manually set on the count rate computer. Division by a constant 60 is performed in order to convert the dimension of CPM x seconds to CPM x minutes, or, simply, counts.

Statement 22 simply performs the addition of the net direct and extrapolated counts, giving the total net absolute count that would

result from the first passage of the isotope, did not the recirculation phenomenon occur.

Statement 23 calculates the amount of radioactivity injected (i.e., the total amount of indicator used); the well background in CPM is subtracted from the CPM/ml of diluted injection. The resultant factor is multiplied by the factor of dilution, giving the actual CPM/ml of material injected; and by the amount of material injected in ml, giving in CPM the net amount of radioactivity injected.

Statement 24 calculates a "calibration factor," which expresses the sensitivity of the external detector to the concentration in CPM/ml of radioactivity in the blood volume seen by the detector. This factor is the ratio between a known concentration (known because measured in an aliquot of blood drawn after mixing) and a known and corresponding external count rate

(known because recorded at the time of withdrawal of blood). Appropriate background values are subtracted from these quantities in each case.

Statement 25 calculates the cardiac output in ml/min, according to equation (10), page 14.

Statement 26 calculates the output in liters rather than in milliliters, because of the established convention of reporting the cardiac index in terms of $L/min/M^2$.

Accordingly, statement 27 calculates the cardiac index. At this point, computation is complete, and all requisite results are contained in memory. Statements 28-37 cause the machine first to name the answer about to be printed, and then to print out the designated answer. It is, of course, possible to have the machine print out any or all of its intermediate or final answers. In the present state of the program, only the major factors of the final equation are asked for, as indicated in statements 44-48 in the program.

VI. STATISTICAL EVALUATION OF THE PROCEDURE

The statistics pertinent to the procedure which are reported in this chapter are drawn from a series of 94 determinations of cardiac output run during the summer months of 1961. Of these 94 determinations, 11 were technical failures, due to one reason or another. Of the remaining 83, 22 were performed as part of a study not sufficiently complete for report at the present time, and 5 were performed on patients in clinical cardiac decompensation, leaving 56 determinations on cardiac normals.

The chief goals of the work which the entire series of determinations represents were the incorporation into the procedure of the technical developments earlier described, standardization of the procedure in humans, and an evaluation of the reproducibility of results in individual

patients, all with a view to producing a workable technic applicable to further problems of cardio-circulatory dynamics. Of the 56 determinations on cardiac normals, 54 were initial runs and repeats on 27 patients. The other two were individual tests on patients who left the hospital before second determinations could be made, and for that reason are omitted from the statistical analysis.

In accord with the purposes outlined above, there follows first an analysis of the determinations run on cardiac normals; to this is appended a brief report of the results of the short series run on patients in clinical cardiac decompensation. This last is included largely out of general interest, since the group is too small to constitute a basis for any hard and fast conclusions.

Repeat determinations on the 27 patients were run in two different ways. With six of these patients, the second determination was made after an interval of 3 or more days. This group is important for the provision of a baseline. Perhaps more important, due to the fact that the procedure would find a special usefulness in situations where determinations are made immediately prior to and following some alteration of the physiologic complex, the repeat determinations on the other 21 patients were made more or less immediately, time elapsed between tests being only sufficient for the technical requirements of the procedure.

From the analysis of the 27 first runs taken as a group, a mean value in terms of cardiac index is found to be 2.95 $L/min/M^2$, with a range of from 1.98 to 3.91, and a standard deviation of 0.55.

The mean values of the two groups constituting the total group of 27 do not vary significantly from the mean value of the total group, being 3.10 for the smaller group of 6, and 2.91 for the larger group of 21. Similarly, the standard deviations of the component groups are essentially similar, being 0.61 and 0.54 respectively.

It is to be noted that these values compare favorably with results obtained with other standard methods of cardiac output determination, and with the results of other investigators who have utilized radioisotopic technics.(4)

When the reproducibility of the procedure is analyzed, it is found that in the group of 6 on whom determinations were made after an interval

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(4) Cf the section on cardiac output in "The Physiological Basis of Medical Practice" by Best and Taylor, Williams and Watkins, 1961, and variously in many of the articles mentioned in the bibliography.

of some days, the second mean for the group was 3.36 as compared to 3.10 as the value of the first mean. This perhaps signifies a tendency for the second outputs to be somewhat higher, presumably due to the complicated changes brought about by retention of isotope in the body and bloodstream, though when the difference is expressed statistically, the standard error of the difference between means is found to be 0.43, and the calculated t value is 0.60, which is not even remotely close to being statistically significant.

When similar comparisons are made between values obtained from the larger group, it is found that the tendency suspected from the results of the series of 6 is more strongly established in the group of 21 immediate repeats. The mean value of the repeat determinations of the large group is 3.35, as compared to a mean value of 2.91 for the first determinations.

The standard error of the difference of means is 0.22; the t value is 2.06, which at 40 df is significant at the 5% level. From this we would have to conclude that with a high degree of probability there is a systematic error in immediate repeats; second runs done immediately tend on the average to give results about 15% higher than do first runs.

If standard deviations of first and second runs in the group of immediate repeats are compared, it is found that the SE of the difference between sigmas is 0.15, the t value being 1.85, which at 40 df is significant at the 10% level. This indicates a greater variability in second immediate runs as compared to first runs, though the increase in variability is not so striking as is the tendency toward higher readings. Whether or not it may become possible to eliminate the tendency towards presumably lesser accuracy in second runs as compared with first runs remains to be seen.

However, it should be noted that absolute values of cardiac output are probably not as necessary for the clinician or researcher as are relative values for the same subject: if the absolute amount of blood pumped per unit time is known approximately, the most uniformly helpful information is to be found in an increase or decrease in cardiac output, either as a result of therapy, or of experimental intervention. Accordingly, assuming the cardiac status of the patients who participated in this study to have been, within the limits of clinical judgment, essentially identical during both runs, it is helpful to compare the level of reproducibility of results from one run to the next in the same patient. The coefficient of correlation which gives a quantitative expression of the tendency for patients with high outputs repeatedly to

give correlatively high readings, and conversely for patients with low outputs, when calculated for the group of six patients turns out to be 0.73; statistically, this indicates a very high degree of relationship. When calculated for the group of 21 patients, the coefficient of correlation is found to be 0.55, which, while not as striking, still denotes substantial or marked relationship. These observations tend to indicate that the procedure as now performed gives a substantially correct estimation of changes in cardiac output, although a degree of systematic error with respect to absolute values is present if repeat determinations are made immediately. It is, in our estimation, of prime import that there exists this level of reproducibility not only when comparisons are made between groups, but when repeat runs are made on the same subject.

The above statistical analyses constitute the substance of this report. However, some additional interesting observations can be made about the patients studied. If the first runs on the total group of 27 patients are considered, and a correlation is calculated between cardiac output in terms of ml/min and the weights of the patients, it is found that r turns out to be 0.62, which indicates marked relationship, as would be expected.

On the other hand, correlation between age and cardiac output in $L/min/M^2$ manifests a slightly negative (and not significant) r value of -0.09, indicating that in this group of patients, who ranged from 28 years to 68 years with a mean age of 47 years, and a standard deviation of 12 years (approximately), there was a slight tendency for the older men to have somewhat lower relative outputs, though this tendency was not marked.

If correlation between age alone and cardiac output in terms of ml/min is made, there is a slightly negative correlation (-0.14), indicating again a slight but statistically insignificant tendency for the older men to pump smaller quantities of blood per unit time.

The brief series of 5 successful determinations run on clinically decompensated patients showed values in terms of cardiac index of 1.42, 1.63, 2.19, 1.65 and 1.76, all of which are quite low, indicating poor circulation; 4 of these values are well outside the entire range of values calculated for presumed cardiac normals. This series of 5 is too small to be the basis of adequate statistical handling, but is included for its general interest, and as an indication of future clinical applications.

VII. SUMMARY OF CONCLUSIONS

1. A technic for estimating cardiac output has been described, the chief advantage of which is its simplicity as far as the patient's role in the procedure is concerned.

2. The results attained by the method are seen to be in good accord with results obtained by other methods.

3. The technical difficulties of the procedure have been simplified by the use of mathematical dimensions not described in the literature before, and by the incorporation of electronic computing into the over-all performance of the procedure.

4. Good correlation has been found to prevail when repeats are run on the same subject.

5. There is a moderate but significant tendency for immediate repeats on the same subjects under similar clinical conditions to give results somewhat elevated over initial readings.

VIII. BIBLIOGRAPHY

1. Beard, E.F. and Wood, E.H., Estimation of Cardiac Output by the Dye Dilution Method with an Ear Oximeter. J. Appl. Physiol., 4:177, 1951.

2. Bernstein, E.F. and Evans, R.H., Evaluation of a New Pulse-Contour Method for the Examination of Cardiac Output. Circulation 24(4):886, part 2, 1961.

3. Bowers, D., Shepherd, J.T., and Wood, E.H., A Constant-Rate Indicator-Infusion Technic for the Measurement of Central Vascular Volume in Man. Canad. J. Biochem. Physiol., 33:340, 1955.

4. Brannon, E.S., Merrill, A.J., Warren, J.V. and Stead, E.A.Jr., The Cardiac Output in Patients with Chronic Anemia as Measured by the Technic of Right Atrial Catheterization., J. Clin. Invest., 24:332, 1945.

5. Cournand, A., Baldwin, J.S. and Himmelstein, A., Cardiac Catheterization in Congenital Heart Disease. Commonwealth Fund, New York, 1949.

6. Cournand, A., Measurement of the Cardiac Output in Man Using the Right Heart Catheterization. Fed. Proc. 4:207, 1945.

7. Cournand, A. and Ranges, H.A., Catherization of the Right Auricle in Man. Soc. Exp. Biol. and Med. 46:462, 1941.

8. Cournand, A., Riley, R.L., Breed, E.S., Baldwin, E.DeF., Richards, D.W.Jr., Lester, M.S. and Jones, M., Measurement of Cardiac Output in Man Using the Technique of Catherization of the Right Auricle or Ventricle. J. Clin. Invest. 24:106, 1945.

9. Crane, M.G., Adams, R. and Woodward, I., Cardiac Output Measured by the Injection Method with Use of Radioactive Material and Continuous Recording. J. Lab. and Clin. Med., 47:802, 1956.

10. Crane, M.G., Sears, C., Hackney, J., Holloway, J. and Collier, C., Cardiac Output Measured by the Injection Method with the Use of Radioactive Material and Continuous Recording. J. Lab. and Clin. Med. 51:248, 1958.

11. Dow, P., Estimation of Cardiac Output and Central Blood Volume by Dye Dilution. Physiol. Rev., 36:77, 1956.

12. Doyle, J.T., Wilson, J.S., Lepine, C. and Warren, J.W., An Evaluation of the Measurement of the Cardiac Output and of the So-Called Pulmonary Blood Volume by Dye Dilution Method. J. Lab. and Clin. Med., 41:29, 1953.

13. Duffy, B.J.Jr., Howley, J.R., Cosma, J. and Hufiuagel, C.A., Cardiac Output in Man Determination by External Counting of RISA., Clin. Res. Proc., 5:94, 1957.

13. Etsten, B and Li, T.H., The Determination of the Cardiac Output by the Dye Dilution Method. Modifications. Comparison with the Fick Method and Application During Anesthesia. Anesthesiology, 15:217, 1954.

14. Feer, van der, Y., Douman, J.H. and Klip, W., Cardiac Output Measurement by the Injection Method without Arterial Sampling. Am. Heart J., 56:642, 1958.

15. Fox,I.J., Sutterer, W.F. and Wood, W.H., Dynamic Response Characteristics of Systems for Continuous Recording of Concentration Changes in a Flowing Liquid (for example, Arterial Indicator Dilution Curves). J. Appl. Physiol., 11:390, 1957.

16. Fox, I.J., Brooker, L.G.S., Heseltine, D.W. and Wood, E.H., A Tricarbocyanine Dye for Continuous Recording of Dilution Curves in Whole Blood Independent of Variations in Blood Oxygen Saturation. Proc. Staff Meet., Mayo Clinic, 32:478, 1957.

17. Fox, I.J., Brooker, L.G.S., Heseltine, D.W. and Wood, E.H., A New Dye for Continuous Recording of Dilution Curves in the Whole Blood Independent of Variations in Blood Oxygen Saturation. Circulation, 14:937, 1956.

18. Fox, I.J., Brooker, L.G.S., Heseltine, D.W. and Wood, E.H., Clinical Applications of a New Dye for Continuous Recording of Arterial Dilution Curves Independent of Variations in Blood Oxygen Saturation. Proc. Thirteenth Scient. Sessions, Am. Heart Assoc., Oct. 25-28, 1957.

19. Freinkel, N., Schreiner, G.E. and Athens, J.W., Simultaneous Determination of Plasma Cardiac Output with Evans Blue and Iodinated Albumin. Am. J. Physiol., 167:785, 1951.

20. Freinkel, N., Schreiner, G.E. and Athens, J.W., Simultaneous Distribution of T-1824 and I-131 Labeled Human Serum Albumin in Man. J. Clin. Invest., 32:138, 1953.

21. Friedlich, A, Heimbecker, R. and Bing, R.J., A Device for Continuous Recording of Concentrations of Evans Blue Dye in Whole Blood and its Application to the Determination of Cardiac Output. J. Appl. Physiol., 3:12, 1950.

22. Fritts, H.W.Jr., Hams, P., Chidsey, C.A.III, Clauss, R.H. and Cournand, A., Estimation of Flow Through Bronchial-Pulmonary Vascular Anastimoses with Use of T-1824 Dye. Circulation, 23:390-8, March 1961.

23. Gilfork, S.T., Gregg, D.E., Shadle, O.W., Ferguson, T.B. and Marzetta, L.A., An Improved Cuvette Densitometer for Cardiac Output Determination by the Dye Dilution Method. Rev. Scient. Instruments, 24:696, 1953.

24. Gorton, R.J., Cardiac Output Responses to Changes in Posture and Exercise. Circulation, 24(4):943, part 2, 1961.

25. Gorton, R.J. and Stauffer, J.C., A Study of the Technics and Sources of Error in the Clinical Application of the External Counting Method of Estimating Cardiac Output. Am. J. Med. Sciences, 238:274, 1959.

26. Groom, A.C., Roberts, P.W., Rowlands, S. and Thomas, H.W., Radioactive Isotopes in Studies on Haemodynamics. Brit. J. Radiol., 32:641, 1959.

27. Guyton, A.C., Farish, C.A. and Nichols, R.J., Continuous Recording of Cardiac Output by the Fick Method. Clin. Res. Procedures, 5:94, 1957.

28. Hamilton, William F., Textbook of Human Physiology, Philadelphia: F.A. Davis Co., 1956.

29. Hamilton, W.F., Moore, J.W., Kingsman, J.M. and Spurling, R.G., Studies on the Circulation, IV; Further Analysis of the Injection Method and of Changes in Hemodynamics under Physiological and Pathological Conditions. Am. J. Physiol., 99:534, 1932.

30. Hamilton, W.F., Notes on the Development of the Physiology of Cardiac Output. Fed. Proc., 4:183, 1945.

31. Hamilton, W.F., Riley, R.L., Attyah, A.M., Cournand, A., Fowell, D.M., Himmelstein, A., Noble, R.P., Remington, J.W., Richards, D.W.Jr., Wheeler, N.C. and Whitham, A.C., Comparison of the Fick and Dye Injection Methods of Measuring the Cardiac Output in Man. Am. J. Physiol. 153:309, 1948.

32. Hetzel, P., Swan, H.F.C. and Wood, E.H., Influence of Injection Site on Arterial Dilution Curves of T-1824. J. Appl. Physiol., 7:66, 1954.

33. Hetzel, P., Swan, H.J.C., Ramirez de Arellano, A.A.R. and Wood, E.H., Estimation of Cardiac Output from First Part of Arterial Dye Dilution Curves. J. Appl. Physiol., 13:92, 1958.

34. Huff, R.L., Feller, D.D. and Bogardus, G., Cardiac Output by Body Surface Counting of I-131 Human Serum Albumin. J. Clin. Invest., 33:944, 1954.

35. Huff, R.L., Feller, D.D., Judd, O.J. and Bogardus, G.M., Cardiac Output of Men and Dogs Measured by in vivo Analysis of Iodinated (I-131) Human Serum Albumin. Circulation Research, 3:564, 1955.

36. Huff, R.L., Parrish, D., Crockett, W. and Haukeness, S., Hemodynamics: Interpreted by Means of Multiple Scintillation Detectors Placed Over the Anterior Thoracic Wall. International J. of Appl. Rad. and Isotopes, 3:85, 1958.

37. Kinsman, J.M., Moore, J.W. and Hamilton, W.F., Studies on Cieculation. I. Injection Method: Practical and Mathematical Considerations. Am. J. Physiol., 89:322, 1929.

38. Lammerant, Jacques and De Visscher, Michel, The Determination of Mean Pulmonary Circulation Time and Pulmonary Circulating Blood Volume in Man with Iodinated (I-131) Human Serum Albumin. Soderbände zur Strahlen-therapie. 36:128-135, 1956.

39. Lapp, Ralph E. and Andrews, Howard L., Nuclear Radiation Physics, New York: Prentice-Hall, Inc., 1954.

40. Lawson, H.C., Cantrell, W.F., Shaw, J.E., Blackburn, D.L. and Adams, S., Measurement of Cardiac Output in the Dog by the Simultaneous Injection of Dye and Radioactive Red Cells. Am. J. Physiol., 170:277, 1952.

41. Li, T.H., Fisher, J.H. and Etsten, B.E., The Determination of the Cardiac Output by the Dye Injection Method. Bull. of the New Eng. Med. Cent., 15:97, 1953.

42. MacCanon, D.M. and Horvath, S.M., Determinations of Cardiac Outputs and Pulmonary Blood Volumes by a Modified Tracer Dilution Procedure. J. Appl. Physiol., 7:413, 1955.

43. MacIntyre, W.J., Pritchard, W.H., Schmidt, W.C., Brofman, B.L. and Moore, D.J., The Determination of Cardiac Output by a Continuous Recording System Utilizing Iodinated (I-131) Human Serum Albumin, II. Clinical Studies. Circulation, 6:572, 1952.

44. McMichael, J., Notes on Cardiac Output Methods. Fed. Proc., 4:212, 1945.

45. Mack, R.E., Wells, H.J. and Pollack, R., An in vivo Method for the Determination of Cardiac Output. Radiology, 68:245, 1957.

46. Meier, P. and Zieher, K.C., On the Theory of the Indicator Dilution Method for the Measurement of Blood Flow and Volume. J. Appl. Physiol., 6:731, 1954.

47. Merrill, A.J., Warren, T.V., Stead, E.H.Jr. and Brannon, E.S., The Circulation in Penetrating Wounds of the Chest: A Study by the Method of Right Heart Catheterization. Am. Heart J., 31:413, 1946.

48. Merriman, J.E., Wyant, G.M., Bray, G. and McGeachy, W., Serial Cardiac Output Determinations in Man. Canad. Anesth. Soc. J., 5:375, 1958.

49. Milnor, W.R., Talbot, S.A., McKeever, W.P., Monge, R.B. and Newman, E.V., A Photoelectric Ear Densitometer for Continuously Recording the Arterial Concentration of T-1824 in the Dye Dilution Method. Circ. Res., 1:117, 1953.

50. Moir, T.W. and Gott, F.S., The Measurement of Central Circulating Blood Volume from Precordial Dilution Curves in Normal Subjects and Patients with Mitral Stenosis. J. Lab. and Clin. Med., 54:926, 1959.

51. Moore, J.W., Kinsman, J.M., Hamilton, W.F. and Spurling, R.G., Studies in Circulation II. Cardiac Output Determinations; Comparison of the Injection Method with the Direct Fick Procedure. Am. J. Physiol., 89:331, 1929.

52. Neely, W.A. and Wilson, F.C., Cardiac Output: A Clinical Comparison of the Direct Fick, Dye and Ballistocardiographic Methods. Surgery, 35:22, 1954.

53. Nicholson, J.W.III, Burchell, H.B. and Wood, E.H., A Method for Continuous Recording of Evans Blue Dye Curves in Arterial Blood and its Application to the Diagnosis of Cardiovascular Abnormalities. J. Lab. and Clin. Med., 37:353, 1951.

54. Norbert, F., Schreiner, G.E. and Athens, J.W., Simultaneous Determination of Plasma Cardiac Output with Evans Blue and Iodinated Albumin. Am. J. of Physiol., 167:785, 1951.

55. Norman, J.A., A Stable Cuvette of High Sensitivity for Indicator Dilution Curves. Brit. Heart J., 21:107, 1959.

56. Nylin, G. and Celander, H., Determination of Blood Volume in the Heart and Lungs and the Cardiac Output through Injection of Radiophosphorus. Circulation. 1:76, 1950.

57. Parrish, D., Hayden, D.T., Garrett, W. and Huff, R.L., Analog Computer Analysis of Flow Characteristics and Volume of the Pulmonary Vascular Bed. Circ. Res., 7:746, 1959.

58. Payne, J.P. and Lyder, B.A., A Comparison of Four Different Methods of Measuring Cardiac Output Used Simultaneously in Anesthetized Dogs. Brit. J. Anaesth., 3:17-21, Jan. 1961.

59. Prinzmetal, M., Corday, E., Spritzler, R.J. and Flieg, W., Radiocardiography and its Clinical Applications. J. Am. Med. Assoc., 139:617, 1959.

60. Pritchard, W.H., MacIntyre, W.J., Schmidt, W.C., Brofman, B.L. and Moore, D.J., Determination of Cardiac Output by a Continuous Recording System Utilizing I-131 Human Serum Albumin. II. Clinical Studies. Circulation Res., 6:572, 1952.

61. Richards, D.W.Jr., Cardiac Output by the Catheterization Technique in Various Clinical Conditions. Fed. Proc. 4:215, 1945.

62. Richardson, D.W., Wyso, E.M., Hect, A.M. and Fitzpatrick, D.P., Accuracy of Continuous Photoelectric Recording of Dye Curves in the Measurement of Cardiac Output. Circulation, 18:770, 1958.

63. Samet, P., Bernstein, W.H. and Silverman, L., Simultaneous Systemic-Arterial and Intra-Cardiac Indicator-Dilution Curves. Circulation, 24(4):1029, part 2, 1961.

64. Sear, H., Allen, T.H. and Gregersen, M.I., Simultaneous Measurement in Dogs of Plasma Volume with I-131 Human Albumin and T-1824 with Comparison of their Long Term Disappearance from the Plasma. Am. J. Physiol., 175:240, 1953.

65. Shadle, O.W., Ferguson, T.B., Gregg, D.E. and Gilford, S.R., Evaluation of a New Cuvette Densitometer for Determining Cardiac Output. Circ. Res., 1:200, 1954.

66. Sheppard, C.W., Mathematical Considerations of Indicator Dilution Techniques. Minnesota Med., 37:93, 1954.

67. Shultz, A.L., Hammarstein, J.F., Heller, B.I. and Ebert, R.V., A Critical Comparison of the T-1824 Dye and Iodinated Albumin Methods for Plasma Volume Measurements. J. Clin Invest., 32:107, 1953.

68. Snyder, J.E., The Cardiac Output and Oxygen Consumption of Surgical Patients Before and After Operation. J. Clin. Invest., 17:571, 1938.

69. Spencer, M.P., Orino, H. and Berry, R.L., Simple Computer Technic for Monitoring Cardiac Output and Peripheral Resistance. Circulation 24(4):1047, part 2, 1961.

70. Starr, I., Present States of the Ballisto-cardiograph as a Means of Measuring Cardiac Output. Fed. Proc., 4:195, 1945.

71. Stead, E.A.Jr., Warren, T.V., Merrill, A.J. and Brannon, E.S., The Cardiac Output in Male Subjects as Measured by the Technique of Right Arterial Catheterization. Normal Values with Observations on the Effect of Anxiety and Tilting. J. Clin. Invest., 24:326, 1945.

72. Stewart, G.N., The Output of the Heart in Dogs. Am. J. Physiol., 57:27, 1921.

73. Stewart, G.N., Researches on the Circulation Time and on the Influences which Affect It. IV. The Output of the Heart. J. Physiol., 7:161, 1897.

74. Stow, R.W. and Hetzel, P.S., An Empirical Formula for Indicator Dilution Curves as Obtained in Human Beings. J. Appl. Physiol., 7:159, 1954.

75. Swan, H.J.C. and Wood, E.H., Localization of Cardiac Defects by Dye-Dilution Curves Recorded After Injection of T-1824 at Multiple Sites in the Heart and Great Vessels During Cardiac Catheterization. Proc. Staff Meet., Mayo Clin., 28:95, 1953.

76. Veall, N., Pearson, J.D., Hanley, T. and Lowe, A.E., A Method for the Determination of Cardiac Output. (Preliminary Report). Radioisotope Conference, 1954, New York: Academic Press, Inc., 1:183, 1954.

77. Warren, J.V., Brannon, E.S., Stead, E.A.Jr. and Merrill, A.J., The Effect of Venesection and the Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observations on Acute Circulatory Collapse in Three Instances. J. Clin. Invest., 24:337, 1945.

78. Warren, J.V., Stead, E.A.Jr. and Brannon, E.S., The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization. Am. J. Physiol., 145:458, 1946.

79. Warner, H.R. and Wood, E.H., Simplified Calculation of Cardiac Output from Dye Dilution Curves Recorded by Oximeter. J. Appl. Physiol., 5:389, 1952.

80. Warren, J.V., Weissler, Q.M. and Leonard, J.J., Observations of the Determinants of Cardiac Output. Trans. Assoc. Am. Phys., 70:268, 1949.

81. Werko, L., Logerlof, H., Bucht, H., Wehle, B. and Holmgren, D., Comparison of the Fick and Hamilton Methods for the Determination of Cardiac Output in Man. Scandinavian J. Clin. and Inves., 1:109, 1949.

82. Wood, E.H. and Swan, H.J.C., Definition of Terms and Symbols for Description of Circulatory Indicator Dilution Curves. J. Appl. Physiol., 6:797, 1954.

83. Virtue, R.W., Caranna, L.J. and Takaoka, K., The Respiratory Pattern and Cardiac Output. Brit. J. Anaesth., 33:77-80, Feb. 1961.