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Serial Determination of Cardiac Output from Precordial Isotope Dilution Curves[1,2]

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INTRODUCTION

Since the introduction of *radiocardiography* by Prinzmetal et al (1) in 1948, many investigators have used radioisotopes in the measurement of blood flow by the indicator dilution principle. In 1952, MacIntyre et al (2) introduced ^{131}I albumin as an indicator for the study of cardiac output. Shortly thereafter, Huff et al (3) compared cardiac outputs estimated from isotope dilution curves, recorded by a detector placed over the anterior chest wall, with determinations based upon the *direct Fick* method. Other studies have compared cardiac output measurements based upon isotope dilution with those obtained by dye dilution (4). Certain reports question the validity of the precordial isotope dilution technique (5). Others report poor agreement between the results of external counting methods and standard methods (6). However, most investigators (7-10) agree that assessment of indicator dilution by external counting is a valid approach. Acceptance of radiocardiography as an aid in clinical investigation has been limited by technical problems involving sensitivity of the detectors, placement of the detector probes, radiation hazards, and dilution curve distortion by time constants of the recording instruments. Also, the dosage of radioactive material required for satisfactory curves has been so high as to preclude serial cardiac output determinations.

The present study was designed to determine: 1, whether satisfactory isotope dilution curves could be recorded over the precordium by using small doses of radioactive indicator, 2, if serial determinations could be made without loss of accuracy, and 3, whether changes in cardiac output could be assessed from precordial dilution curves.

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METHODS

Healthy volunteers and hospitalized patients of both sexes, ranging in age from 16 to 80 years, were fluoroscoped or had a standard P-A chest film to determine the point at which the ascending aorta clears the cardiac silhouette. The projection of this area on the anterior chest wall was marked with a wax pencil.

With the subject supine, using local two per cent Xylocaine anesthesia, an 18-gauge Cournand needle was secured in the brachial artery. Polyethylene tubing with an internal diameter of 0.085 inches was used to connect the Cournand needle with a Gilford infrared-sensitive densitometer and a constant-rate withdrawal pump. Arterial dye-dilution curves were inscribed on a Texas Instruments rectilinear recorder. Blood clotting was prevented by prior irrigation of the tubing with dilute, sterile, heparin solution.

A 3 × 2 inch NaI (Tl) scintillation detector, fitted with a flat field collimator, was centered perpendicularly over the mark corresponding to the ascending aorta. The collimator had a three-inch diameter and the length was such as to provide a 7.5-inch distance from the anterior chest wall to the crystal face. The detector probe was locked in position and the subject was instructed to lie quietly. Pulses produced by the 364 keV gamma ray from ^{131}I were selected by a single-channel pulse-height analyzer and a ratemeter was driven by the output of the analyzer. The output was also simultaneously recorded on magnetic tape, which permitted reproduction of curves using different ratemeter ranges and time constants.

Following the rapid intravenous injection of a bolus of indicator consisting of cardiogreen-RISA ^{131}I, dilution curves were inscribed. The count rate corresponding to the final concentration of isotope in the blood was recorded over a period of at least three minutes, starting seven minutes after injection of the indi-

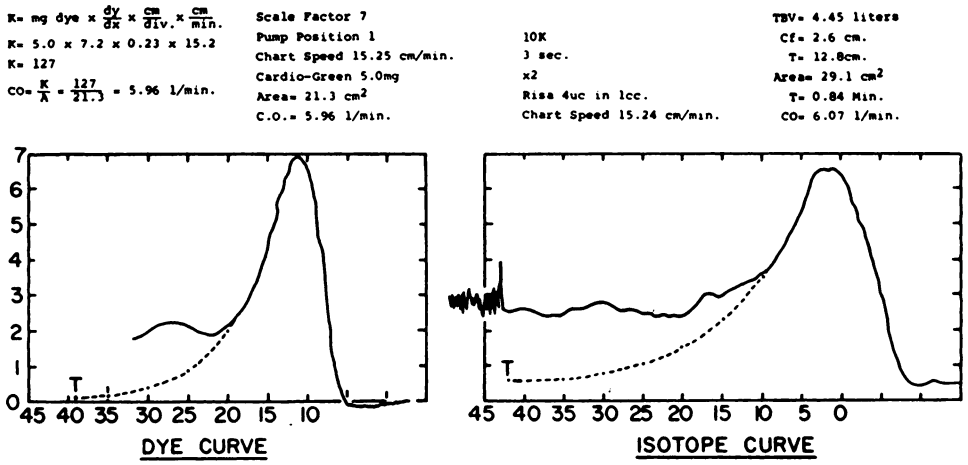

Fig. 1. These curves, left = arterial dye dilution; right = precordial radioisotope dilution, were recorded simultaneously after intravenous injection of a single bolus containing indocyanine green dye and RISA ^{131}I.

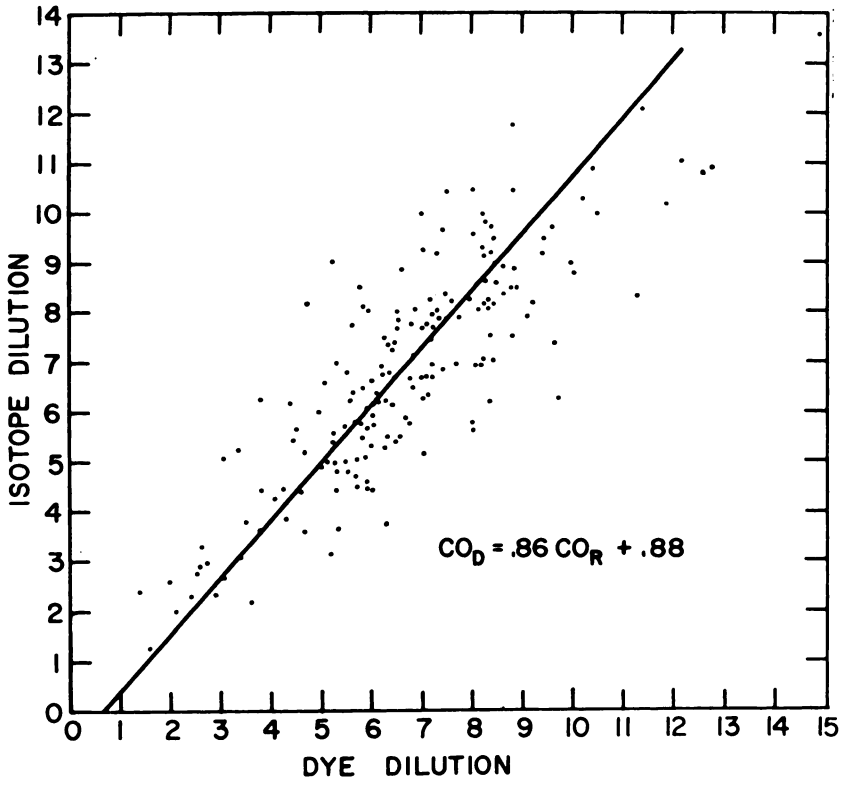

Fig. 2. Comparison of values for cardiac output obtained from analysis of simultaneously recorded arterial dye dilution and precordial radioisotope dilution curves. The soild line represents the calculated linear regression curve for these data.

cator. At the end of this sampling period, a sample of blood was drawn for the determination of total blood volume, with the aid of a blood-volume computer. Heart rate was calculated from the electrocardiogram, and blood pressure was measured with a cuff sphygmomanometer.

In 63 patients two or three successive cardiac-output determinations were made without induction of hemodynamic changes. One ml of cardiogreen, 5.0 mg/ml, was injected in all cases, while the RISA ^{131}I activity was 4μC for the first injection and was increased by 4 μC for each subsequent injection. Nine patients received 2 mg of atropine sulfate intravenously, after baseline cardiac outputs were obtained. Following the drug administration, the determination of cardiac output was repeated at or near the peak of atropine induced tachycardia.

Cardiac output was calculated from the dye dilution curves according to the Stewart-Hamilton principle (11, 12), using the following equation:

$$C.O. = \frac{I}{\int_0^\infty C(t)d(t)}$$

where CO = cardiac output (L/min)

I = injected dye (mg)

C(t) = concentration of dye in arterial blood (mg/L)

The integral is evaluated by measuring the area under the extra polated dye dilution curve. An adaptation of the above equation was used for the isotope dilution curves (13):

$$CO = \frac{C_f \times TBV \times V}{A}$$

where C_f = precordial counting rate after complete mixing (cm on chart paper)

TBV = total blood volume (liters)

A = area under the extrapolated time-activity curve $(cm)^2$

V = chart speed (cm/min).

The majority of isotope dilution curves were recorded with a time constant of three seconds.

RESULTS

In 103 subjects, 192 simultaneous pairs of dilution curves were recorded. A total of 180 satisfactory pairs of curves was obtained. One such pair of curves is shown in Figure 1. Values for cardiac outputs calculated from the simultaneously inscribed curves are plotted in Figure 2. The equation of the linear regression line was:

$$CO_D = .86\, CO_R + .88$$

where

CO_R = cardiac output by isotope dilution

CO_D = cardiac output by dye dilution

When the 180 pairs of curves were viewed as a group the mean values of cardiac output plus or minus the standard error of the mean were as follows:

Dye dilution 6.79 ± 0.18 L/min

Isotope dilution 6.88 ± 0.16 L/min

The correlation coefficient for the group is 0.80. The paired t-test was performed to test for significant differences between the pairs and was 0.75. The variations between the two methods are presented in Table I.

TABLE I

VARIATION BETWEEN DYE AND ISOTOPE VALUES

Percent of Variation	*Number of Curves*	*Range of Variation*
Less than 5%	50	0.1– 4.9
5 to 10%	33	5.4–10.0
10 to 15%	34	10.2–15.0
15 to 20%	13	15.3–19.1
20 to 25%	12	20.7–24.5
Over 25%	38	25.2–76.4

In 47 subjects serial determinations of cardiac outputs were performed while the subjects were at rest. In 36 volunteers two pairs of curves were recorded successively; in 25 subjects three pairs of curves were obtained. Since complete mixing of the isotope had to be attained for the recording of the final concentration, which generally takes ten minutes, the curves were inscribed at intervals ranging from 11 to 15 minutes. The correlation coefficient when two successive pairs of curves were obtained was 0.68 for the first pairs and 0.84 for the second pairs. When three successive pairs of curves were obtained, the correlation coefficients were 0.61, 0.82 and 0.75, respectively. The means, standard error of the means, t-values, for these serial data are given in Table II.

Measurements from nine subjects, who were given 2 mg of atropine sulfate, in order to alter their hemodynamic status, are summarized in Table III. The means of the cardiac output values from the paired curves recorded during the atropine experiments were as follows:

Control RISA $^{131}I = 6.74 \pm 0.42$ Control dye $= 6.47 \pm 0.26$

RISA ^{131}I after atropine $= 8.56 \pm 0.45$ Dye after atropine $= 8.59 \pm 0.36$

The nonpaired t for the values obtained from the isotope dilution curves before and after the drug administration was 2.92. The nonpaired t for the values calculated from dye dilution curves before and after atropine was 4.81. The paired t-value for eight degrees of freedom was 1.05 for the control data and 0.14 for the data after the atropine administration.

DISCUSSION

In the work described by many authors (9, 14-18), doses of radioactive indicator ranging from 20-500 μC have been used to obtain precordial dilution curves from which cardiac output can be satisfactorily estimated. In the present study it has been shown that reliable data can be obtained using doses of RISA ^{131}I as low as 4 microcuries. This increase in method *sensitivity* has been primarily achieved by using larger crystal dimensions compared to those employed elsewhere (19-21). Four μC also proved to be convenient because this dose did not exceed the capacity of the blood volume computer. The results obtained with such doses are comparable to those reported (22).

The technique of other investigators has been applied in the present study to the serial determination of cardiac output, *i.e.* the dose of radioactive indicator was doubled for the second determination (9, 20, 21). For a third determination an increase of 50% of the second dose proved sufficient. With this dosage schedule, serial determinations were carried out. As can be seen from Table II, when two successive determinations were carried out, the paired t-value for the first pair of curves indicated a significant difference between the two methods. This difference, however, became insignificant for the second pair of curves. Although the explanation for this finding is not apparent from the data, accuracy of some of the earlier determinations might have suffered from technical inadequacies. Later in the series, longer periods of adjustment to the surroundings were allowed to each subject. Also, the probe position was determined from a standard P-A chest film in the early experiments; recently we have made ex-

TABLE II

COMPARISON OF THE METHODS FOR SERIAL DETERMINATION OF CARDIAC OUTPUT

Cardiac Output (L/min)

	Two Successive Pairs		*Three Successive Pairs*		
	1st Pair	*2nd Pair*	*1st Pair*	*2nd Pair*	*3rd Pair*
N	36	36	25	25	25
Dye–Mean ± SEM	6.63 ± 0.26	7.59 ± 0.29	6.81 ± 0.28	7.84 ± 0.80	7.75 ± 0.30
^{131}I–Mean ± SEM	7.21 ± 0.30	7.82 ± 0.35	7.24 ± 0.30	8.00 ± 0.29	7.59 ± 0.32
Paired t	2.49[1]	1.22	1.65	0.87	0.72

[1]Statistically significant

t-values, and the regression equations for these serial data are given in Table II. clusive use of fluoroscopy with the subject in the supine position. The latter approach assured a more precise placement of the detector probe. It is of interest that measurements taken from the fluoroscoped group show insignificant differences between the two methods in any pair. Agreement between the two methods improved for the second and the third set of curves. The basis for the better correlation is not clear, but it would seem likely that adjustment of the subjects to the environment is a significant factor. Over-all, these data attest to the feasibility of serial cardiac output determinations by the precordial isotope dilution method.

In order to test the ability of the method to measure cardiac output under conditions of altered hemodynamics, tachycardia was produced by the intravenous administration of 2 mg of atropine sulfate. All nine subjects tested had an increase in heart rate ranging from 32 to 60 beats per minute. In all nine subjects the administration of atropine brought about an increase in cardiac output, which was demonstrated by both the dye and isotope method. Thus, qualitative changes in cardiac output can reliably be estimated by the precordial isotope method. A quantitative correlation between the two methods was obtained under these experimental conditions; there was no statistically significant difference between the isotope and dye control values, and the isotope and dye values after the drug administration in this small series. However, statistically significant differences were found by both methods between the cardiac output before and after the administration of atropine.

In these experiments, we noted several sources of error in the measurement of cardiac output by the precordial isotope dilution method. Most of the pitfalls are avoidable. Improper probe placement was a frequent cause of poor curves. Paravenous injection of the indicator, and errors in blood-volume measurement were experienced on occasion. Curves from patients with an enlarged

TABLE III

HEMODYNAMIC EFFECTS OF ATROPINE SULFATE (2 MG, I.V.)

Cardiac Output (L/min)		*Cardiac Output (L/min)*		*Heart Rate (beats/min)*		*Arterial Blood Pressure (mm Hg)*	
Before	*Cardio-*	*After*	*Cardio-*				
RISA ^{131}I	*green*	*RISA* ^{131}I	*green*	*Before*	*After*	*Before*	*After*
7.47	6.33	9.18	8.33	—	—	120/70	120/80
5.40	5.31	8.26	7.93	58	100	110/70	130/85
6.95	6.24	8.50	8.79	64	124	135/75	155/95
6.47	6.84	7.90	7.80	92	124	120/75	120/75
5.37	6.56	7.05	8.24	68	115	115/70	130/80
6.19	6.05	7.94	9.14	65	115	130/70	140/75
7.39	6.51	8.23	8.34	83	125	—	—
5.75	6.02	7.92	7.41	84	110	130/80	130/90
9.69	8.42	12.10	11.40	70	110	130/70	140/70

heart were often impossible to interpret. Deformities of the chest and unsuspected venous occlusions were encountered, resulting in failure to inscribe satisfactory precordial dilution curves. The use of the method was limited in patients with pronounced cardiac arrhythmia and in patients with congestive heart failure, who had unusually slow peripheral circulation.

Despite its limitations, the method of estimating cardiac output from precordial isotope dilution curves should have useful application in many situations when arterial cannulation should be avoided.

SUMMARY

In 103 subjects, 192 pairs of dilution curves utilizing indocyanine green and RISA ^{131}I were recorded simultaneously. 180 satisfactory pairs of curves were obtained. The corelation between the two methods was good as evidenced by a correlation coefficient of 0.80. Serial determinations were carried out under basal conditions. Satisfactory agreement was obtained for second and third set curves. Atropine-induced changes in cardiac output could be demonstrated by both methods.

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The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be submitted if no tables or illustrations are required. Only the minimum number of references should be cited.

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