Value of Continuous Photoelectric Recording of Dye Curves in the Estimation of Cardiac Output

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In order to test photoelectric recording of dye curves, simultaneous determinations of cardiac output were made in 48 patients with heart disease with the Fick and dye-dilution techniques. The dye curves were recorded with a Colson densitometer following either intrathoracic or antecubital injection of dye. Both Evans blue and indocyanine green dyes were employed. Satisfactory agreement was noted between Fick and dye estimates, demonstrating empirically the usefulness of the continuous recording technic.

A VAILABILITY of a cuvette densitometer, allowing continuous recording of the concentration of Evans blue dye in the blood, has simplified methodology for estimation of cardiac output by the dye-dilution technic. The classic Hamilton dye-dilution method with intermittent sampling and measurement of dye concentration in plasma has been repeatedly shown to compare closely with the Fick technic for measurement of cardiac output in normal human subjects, and in patients with heart disease, but photoelectric recording of changing dye concentration in whole blood has been criticized, particularly because of the variable optical properties of flowing blood. The present study was undertaken to compare estimates of cardiac output obtained by the Fick and dye-dilution technics, the latter utilizing a densitometer that continuously recorded the concentration of dye in whole blood. Comparisons were also made between intra-thoracic and arm-vein injection of dye.

METHODS

Subjects were 48 hospital patients with cardiovascular disease ranging in age from 25 to 72 years and in functional classification from I to III. None was dyspneic at rest at the time of catheterization. No premedication was given; procaine 1 per cent was used at the sites of phlebotomy and of the intra-arterial needle. All subjects breathed room air.

In a typical experiment the catheter was introduced into the pulmonary artery and a needle was inserted into a brachial artery. Blood samples for calibration of the densitometer were withdrawn from the brachial artery. A 15-minute rest period was then allowed, following which cardiac output measurements were performed. When possible, a Fick determination and a dye curve were followed by another Fick determination and dye curve, performed as rapidly as was possible, usually within 30 minutes.

Dye was injected through a calibrated syringe-needle or syringe-catheter system. For recording dye-dilution curves, blood was drawn from the brachial artery through a Cournand needle, a polyethylene tube 4 inches in length with inside diameter of 0.75 mm. (Clay-Adams PE 60), and through the cuvette of a standard Colson Model-103 densitometer. The volume between the tip of the arterial needle and the outflow from the cuvette was 0.9 ml. The internal volume of the cuvette was 0.04 ml. Blood was drawn through the cuvette at rates of 0.6 to 0.8 ml. per second. The Colson densitometer consists of (1) an incandescent bulb light source; (2) Bausch-Lomb interference filters for selection of light with wavelength of 630 mμ, the maximum absorption wavelength of Evans blue, or of 800 mμ, the peak absorption wavelength of indocyanine-green dye; (3) a cuvette through which blood passes, made of 2 plane glass surfaces 1.0 mm. apart, with exposure of a channel ⅛ by ⅜ inches through which light passes from light source to photomultiplier; and (4) a photomultiplier (RCA 931A) with associated electronic circuitry to provide output voltage linearly proportional to optical density of solutions in the cuvette.

Two different calibration systems were used in

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the studies reported. All results regarding measurements of cardiac output using Evans blue dye were derived from curves calibrated as follows: prior to the measurement of cardiac output in each patient 100 ml. of arterial blood were collected anaerobically in a mercury-filled sampling tube. Twenty-milliliter lots of this undyed blood were transferred anaerobically to oiled syringes, and a known volume of 5 per cent Evans blue dye was then added from a calibrated Krogh-Keys pipette through a long, no.-26 needle into each syringe. For each patient, these anaerobically prepared samples, one of which was undyed and 3 of which contained varying concentrations of dye, were then pulled through the same needle, tubing, and cuvette, with use of the same falling-mercury sampling system. Rate of blood flow through the cuvette was, therefore, the same during calibration as during recording of the dye curves. From these anaerobically collected blood samples a graph of the relation between dye concentration and recorder deflection was plotted. From this relation a factor was derived that was used to convert millimeters of recorder deflection to concentration of dye.

In the studies using indocyanine-green dye, a syringe pump capable of drawing blood through the Colson cuvette at a constant rate was employed, and measurements made with green dye were calibrated according to a method described by Theilen et al. similar to that used by Enmanuel, Lacey, and Newman.

Figure 1 demonstrates the linear relation between deflection of the cuvette-recorder system and concentration of indocyanine-green dye in both plasma and whole blood. Similar linearity was observed with Evans blue dye.

Fick gas collections were made over 5- or 6-minute periods with use of a nose clip, mouthpiece, and Douglas bag. Arterial and mixed venous samples were collected anaerobically over a 1-minute period in the middle of the gas collection. Blood samples were analyzed in duplicate for oxygen by the technic of Van Slyke and Neill. Expired gas was analyzed for carbon dioxide and oxygen by the Scholander apparatus, and oxygen consumption was calculated by the method of Haldane and Priestly. Intra-arterial pressure was recorded before the first and after the last output determinations. No significant differences in blood pressure or in hematocrit value occurred between the first and last output measurements in a given individual.

**RESULTS**

Fick determinations were compared with intrathoracic dye injection in 54 studies in 36 patients (fig. 2). Good agreement between individual Fick and dye estimates was found. In 43 of the total 54 comparisons, cardiac index estimated by dye dilution was within 12.5 per cent of the Fick estimate, and in no case was the difference greater than 25 per cent. Average cardiac index determined by the Fick method was 2.44 L. per minute per M. and by the dye method the average value was 2.36 L. per minute per M. The averages of the two methods differed by 0.08 L. per minute per M. (3 per cent). Standard deviation of the individual differences between repeat determinations of cardiac out-
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Fig. 2 Top. Comparison of cardiac index measured by indicator-dilution with nearly simultaneous estimates by the Fick method in the same subjects. Heavy line joins points indicating equal estimates by both methods. The difference between the means is 3 per cent (0.08 L per minute per M²) of the Fick mean, and the standard deviation of the individual differences between Fick and dye values is 0.29 L per minute per M².

Fig. 3 Middle. The reproducibility of the Fick measurement. Points, comparison of an estimate of cardiac index by the Fick method with another estimate by putting in the same patient by the Fick method and by the dye method was 0.29 L per minute per M.² The means were not significantly different as evaluated by the standard Fisher t test.

The variability between 2 Fick determinations in the same subject was about the same as that between 2 successive dye estimates. Figure 3 compares the cardiac index obtained by the first Fick estimate with that by the second Fick estimate in the same patient. Figure 4 shows similar comparisons of 2 dye estimates in the same subject.

The continuous densitometric recording method used in these studies was compared with the classic intermittent sampling technic of Hamilton in 2 experiments. Dye was injected into the pulmonary artery. The densitometer continuously recorded dye concentration in brachial artery blood, while at the same time intermittent samples were collected from a femoral artery at 2-second intervals through a no. 17 needle and 3-inch length of Clay-Adams polyethylene 190 tubing. Plasma from each of the intermittent samples was diluted 1:9, and concentration of indocyanine-green dye was measured with a Beckman model B spectrophotometer. Figure 5 shows the curves of plasma dye concentration obtained by both technics and demonstrates close agreement observed in both trials.

Measurement of cardiac output by injection of dye into an antecubital vein was compared with estimates by the Fick method, in order to explore further the value of arm-vein dye injection in estimation of cardiac output. Dye was injected through a no. 15
or 17 needle and was followed immediately by 20 ml. of saline solution to propel the bolus of dye promptly into the central circulation. Figure 6 demonstrates the comparison of antecubital dye injection and Fick estimates of cardiac index. In 14 of 20 determinations, cardiac index measured by forearm dye injection was within 12.5 per cent of the Fick index, and in no instance was the difference between the 2 so great as 25 per cent. In 11 of the 20 determinations the Fick estimate was higher than the dye value, but average values were not significantly different. (Fick, 2.42 L per minute per M$^2$; dye, 2.25 L per minute per M$^2$)

Following arm-vein dye injection, circulation time (to peak of curve) averaged 28 seconds, with individual values ranging from 18 to 57 seconds. These values were distinctly more prolonged than circulation times obtained with intrathoracic dye injection, which averaged 18 seconds, individual determinations varying from 10 to 27 seconds. Although there was definite correlation between circulation time and cardiac output in the entire group, figure 7 demonstrates the wide variation in cardiac index associated with any given value of circulation time.

Indocyanine-green dye has been administered to 45 patients in these and related studies. Individual doses have ranged from 5 to 15 mg., and total doses in individual patients have reached 60 mg. The dye has produced no toxic effects, nor has skin discoloration been observed. Green color, detectable by the densitometer, disappeared from the plasma in 15 minutes. Observations of urine sediment, serum bilirubin, white blood count, and hematocrit level, made 20 hours following multiple injections of the dye in 10 individuals, showed no change from preinjection values.

**Fig. 5 Top.** Dye-dilution curves obtained by continuous and intermittent sampling technics. Each pair of curves records simultaneous determinations by the 2 technics in a given subject.

**Fig. 6 Middle.** Comparison of cardiac index estimates from antecubital vein dye injection (horizontal axis) with estimates obtained by Fick method in the same subjects. Mean of the dye values was 2.3 L per minute per M$^2$. Average of the Fick determinations was 2.3 L per minute per M$^2$. Standard deviation of the differences between individual determinations was 0.28 L per minute per M$^2$.

**Fig. 7 Bottom.** Relation between circulation time and cardiac index. Circulation times are the times from intrathoracic dye injection to the peak of the dye curve. Cardiac indexes are those calculated from the same dye curve in which the circulation time was measured.
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DISCUSSION

The data demonstrate satisfactory agreement between dye and Fick estimates of cardiac output in patients with heart disease, and suggest that densitometric recording is sufficiently accurate for practical purposes. Table 1 presents data available in the English literature comparing Fick with dye estimates. In addition, Ring et al., 15 have presented comparison of the Wood cuvette oximeter with the intermittent-sampling technic for measurement of cardiac output by dye dilution. They demonstrated good agreement, in 24 comparisons in 12 subjects, the difference between the 2 methods averaging 2 per cent. No individual difference exceeded 8 per cent.

These empiric demonstrations of close agreement between 2 quite different approaches to measurement of cardiac output buttress the solid theoretic bases of each method to lend support to the conclusion that both technics accurately estimate the volume of blood pumped by the heart. In individual subjects, slight differences between Fick and dye estimates are not surprising, since the dye method records average output during a 30-second period, while the Fick procedure calculates average cardiac output for a 5-minute period. Close agreement between successive Fick and dye determinations implies a remarkably steady state existing during the 30 minutes required to record 2 Fick and 2 dye measurements.

Advantages of Densitometric Measurement. The greatest single advantage of photocell recording of dye-dilution curves over the classic intermittent-sampling method of Hamilton lies in the ability of the investigator to visualize the curve as it is sampled rather than hours later. Unsatisfactory curves can be repeated at once. The sensitivity of the instrument has allowed routine recording of excellent curves following injection of only 10 mg. of Evans blue dye, permitting 4 successive determinations of cardiac output in the same subject without blue discoloration of the skin. Convenience in recording the dye curv and reduction of blood lost during sampling represent further advantages of densitometer recording. The small volume of the cuvette (0.04 ml.) allows complete replacement of the blood in the cuvette many times in each second, so that a very large number of individual values of dye concentration are available for plotting. This factor is of particular value in rapidly changing dye curves, for instance in the localization of right-to-left intracardiac shunts.

Disadvantages. The most serious disadvantages of this method centered around the calibration procedure used with Evans blue dye. About 100 ml. of blood were collected from each subject for calibration purposes. Addition of 0.2 ml., 0.4 ml., and 0.6 ml. of 5 per cent Evans blue to 20 ml. of blood gave optimal deflections in the recording system used. Accurate delivery of these small volumes of dye into the blood under anaerobic conditions represented a difficult problem. In an annoying minority of the determinations, perfectly good dye curves could not be used

<table>
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<th>Authors</th>
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<th>Average cardiac index (L./min./M.2)</th>
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<tr>
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<td>3.06</td>
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<td>39†</td>
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<td>48‡</td>
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<td>Werko§</td>
<td>69§</td>
<td>3.39</td>
<td>3.53</td>
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<tr>
<td>Kopelman and Lee¶</td>
<td>28¶</td>
<td>2.54</td>
<td>2.54</td>
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<td>Nicholson‖</td>
<td>8‖</td>
<td>2.61</td>
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<td>Friedlich**</td>
<td>9**</td>
<td>3.40</td>
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<tr>
<td>Present series</td>
<td>48</td>
<td>2.44</td>
<td>2.36</td>
</tr>
</tbody>
</table>

* Fifty-three normal, 25 with heart disease, functional classes I-IV.
† Twenty-two normal subjects.
‡ Seven normal and 24 patients with heart and lung disease. Six determinations during exercise.
§ Six normal; rest hypertensive, rheumatic heart disease, cor pulmonale, functional classes I-IV.
¶ Ten normal, 10 rheumatic heart disease with mitral stenosis, 8 with left ventricular failure.
‖ Data given by authors for cardiac output only. Figures presented are authors' means divided by 1.73.
** "Patients with cardiovascular abnormalities." Dye curves recorded continuously.

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for calculation of cardiac output because of obviously nonlinear calibration. A sufficient number of calibrations was recorded in which a straight line connected the origin and 3 dye concentrations to indicate that deflection of the recorder was linearly related to dye concentration in whole blood, and that nonlinear calibration was caused by errors in pipetting the dye. The disadvantages, inherent in this calibration procedure, led in the more recent measurements using green dye, to the use of the calibration method of Theilen et al.\textsuperscript{11} in which blood collected during actual inscription of the dye curves is used for calibration, with reduction of blood shed and avoidance of pipetting errors.

Agreement between Fick estimates of cardiac output and those obtained by antecubital dye injection reemphasizes an additional advantage of the dye method; namely, its usefulness in patients in whom cardiac catheterization is inconvenient or inadvisable. Dye curves tend to be more spread out and to have lower peaks as the injection site is moved farther from the sampling site,\textsuperscript{16} and occasionally curves obtained by arm-vein injection are so flat as to be useless, particularly in patients with marked valvular regurgitation or great increase in pulmonary blood volume. In such instances, a larger dose of dye may prove useful, but intrathoracic injection of dye is often necessary.

Indocyanine-green dye\textsuperscript{10} has proved nontoxic, of good optical density, and easy to handle. Its chief advantage over Evans blue dye lies in the fact that it may be administered repeatedly without skin discoloration. Both its color and the rapidity with which it is cleared from plasma contribute to this useful feature. A second advantage of indocyanine-green dye relates to its wavelength of maximum light absorption, 800 m\textmu, a wavelength at which oxygenated and reduced hemoglobin absorb light equally. With the densitometer filters chosen to transmit to the photocell light of this wavelength, the output of the photocell is practically independent of the oxygen saturation of the blood. The densitometer, therefore, recognizes changes in hemoglobin saturation very poorly, and dye curves are uninfluenced by marked fluctuation in the oxygen content of the blood. Fading of color and aggregation of dye particles have not been a problem if green dye is dissolved first in the diluent supplied with the dye and then in plasma. Fading is rapid in water or saline solutions.

**Summary**

Continuous recording of dye concentration in blood by means of a photoelectric densitometer has proved a convenient technic for estimation of cardiac output by the indicator-dilution principle. Comparison of this technic with the Fick method has demonstrated close agreement in 48 human subjects with heart disease. Though most of the dye curves were produced by intracardiac dye injection, antecubital vein injection also produced estimates of cardiac output that compared favorably with nearly simultaneous Fick estimates.

The close agreement observed empirically between these widely different approaches to measurement of cardiac output supports the theoretic bases of the 2 methods in suggesting that cardiac output can be accurately estimated in the intact human, with ease and convenience.

**Acknowledgment**

The authors wish to thank Dr. W. T. Thompson, Jr., for criticism and advice, and Mrs. D. S. Clark and Gordon Cavell for performing many of the cardiac catheterizations. The expert technical assistance of Mrs. Marjorie Stephenson, Mrs. Eunice Donald, and Misses Carol Aloxck and Mary Andre is gratefully acknowledged. Indocyanine-green dye was supplied as “Cardiogreen” through the courtesy of Dr. John Brewer of Hynson, Westcott, and Dunning, Baltimore, Md.

**Summario in Interlingua**

Le registração continue del concentration de colorante in le sanguine per medio de un densitometro photoelectric se ha provate un convenibile technica in le estimación del rendimento cardiac super le base del principio del dilution de indicatore. Le comparation de iste technica con le metodo de Fick in 48
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subjectos human con morbo cardiac ha demostrate un alte grado de concordantia. Le majoritate del curvas de colorante eseva basate super injectiones intracardiac, sed injectiones in venas antecubital resultava etiam in estimationes de rendimento cardiac ben comparabile con illos de quasi simultaneae estimationes secundo le metodo de Fick.

Le intime concordantia empiricamente observe inter iste differentissime methodos pro le measurement del rendimento cardiac supporta le bases theoret de ille methodos. Le ultime conclusion practic pare esser que le rendimento cardiac pote esser determinate accuratamente in humanos intacte e que le procedimentos technic que es requisit in tal determinationes es facile e convenibile.

REFERENCES

Value of Continuous Photoelectric Recording of Dye Curves in the Estimation of Cardiac Output
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Circulation. 1959;20:1111-1117
doi: 10.1161/01.CIR.20.6.1111

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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