Errors in the Processing of Dye Dilution Curves

By G. Richard Kelman, M.B., Ch.B., M.Sc., D.I.C.

The measurement of cardiac output by the dye dilution technique has become well established both in routine clinical practice and also as a research tool. In the usual method, a bolus of dye is injected rapidly into the venous side of the circulation, and the resulting change of dye concentration is measured as a function of time at some distal site in the arterial system. The cardiac output is then calculated from the formula:

\[ Q = \frac{60 \ m}{\int_0^t c(t) \ dt} \]

where \( Q \) = cardiac output (liters/minute), \( m \) = mass of dye injected.

\[ \int_0^t c(t) \ dt = \text{the area under the curve of arterial dye concentration plotted against time (seconds) after correction for recirculation.} \]

It is also common practice to calculate the vascular volume \( V \) lying between the injection and sampling sites using the equation:

\[ V = Q \ t = \frac{\int_0^t t \ c(t) \ dt}{\int_0^t c(t) \ dt} \]

The validity of these formulas has been demonstrated by Zierler, but an enquiry into the methods used in various centers for evaluating the two integrals showed that the possible errors in this calculation were imperfectly understood. This paper is an attempt to define these errors and to suggest how they may be reduced to a minimum.

Theory

To determine the area under a curve, it is necessary either to know the equation of the curve so that the integration may be performed analytically, or else to perform the integration numerically. In general, the equations of dye dilution curves are not known, so it is necessary to resort to numerical integration techniques. Since the various formulas which are available for this purpose do not appear to be widely known to medical workers they will be reviewed briefly here.

In textbooks on numerical analysis many integration formulas are described, but the data involved in cardiovascular investigations are such that it will be sufficient to consider here the two simplest formulas. These are known respectively as the trapezoid rule and Simpson's rule.

a) TRAPEZOID RULE

Suppose we wish to determine the area shown in figure 1a. If we measure the ordinates at equally spaced intervals of time \( \Delta t \), and approximate the curve in between these ordinates by straight lines as in figure 1b, then this new area is an approximation to that in figure 1a. The smaller the sampling time interval \( \Delta t \) the more accurate is the approximation. The area in figure 1b is easily seen to be

\[ \left( \frac{y_0 + y_1}{2} + \frac{y_1 + y_2}{2} + \frac{y_2 + y_3}{2} + \frac{y_3 + y_4}{2} + \frac{y_4 + y_5}{2} \right) \Delta t \]

\[ = \left( \frac{y_0 + y_1 + y_2 + y_3 + y_4 + y_5}{6} \right) \Delta t \]

where \( y_0, y_1, y_2, \ldots, y_5 \) are the successive ordinates.

In the general case we have

\[ \int_{t_0}^{t_n} y(t) \ dt \approx \left( \frac{y_0 + y_1 + \ldots + y_{n-1} + y_n}{2} \right) \Delta t \]

It is shown in texts on numerical analysis that
Using this approximation it may be shown that
\[
\int_0^1 y(t) \, dt \approx \frac{1}{3} \left[ y_0 + 4(y_1 + y_2 + \ldots + y_{n-2}) + 2(y_2 + y_4 + \ldots + y_{n-1}) + y_n \right] \Delta t
\]

The error involved in the approximation is less than \( \frac{\Delta t^4}{90} (t_n - t_0) y''''(u) \), where \( y''''(u) \) is the greatest numerical value of the fourth derivative of \( y(t) \) in the interval \( t_0 < t < t_n \).

Before it is possible to calculate cardiac output or vascular volume from a dye dilution curve it is necessary to eliminate the effects of recirculation. Kinsman et al. showed in 1929 that, before the occurrence of recirculation, the down limb of a typical dye curve falls exponentially towards zero dye concentration. If the dye curve is replotted therefore, on semilogarithmic graph paper, the part of the curve which is decaying exponentially becomes linear, and it is possible to eliminate the effects of recirculation by extrapolating this linear part of the curve down to low dye concentrations.

An alternative and more attractive method is to determine the decay constant of the exponential fall by measuring the gradient of the straight line on the semilog plot. The area under this part of the curve may then be calculated analytically. It is
\[
c' \int_{t'}^\infty e^{-k(t-t')} \, dt = c'/k,
\]
where \( c' \) is the dye concentration at the point when the exponential decay begins, \( t' \) is the time of occurrence of this ordinate, and \( k \) is the decay constant. In a similar way it is possible to determine the first moment for this part of the curve. It is
\[
c' \int_{t'}^\infty (t-t')e^{-k(t-t')} \, dt = c'/k^2.
\]

The mean transit time for the whole curve may then be determined by combination of the integrals with those for the first part of the curve. These are conveniently evaluated by numerical integration.

**Methods**

Errors in the processing of dye dilution curves were studied in 12 cardiac output curves both normal and abnormal. No special criteria were used in the selection of the curves but a wide variety of shapes was included. The trapezoidal rule and Simpson’s rule were used to calculate the areas under the curves up to the point at which the concentrations began to fall exponentially. The ordinates were measured at one-second intervals. These areas were also measured using numerical integration.
a planimeter. The integral \( \int t c(t) \, dt \) was calculated using Simpson's rule and the trapezoid rule.

The decay constant of the part of the curve which was decaying exponentially was determined in the usual way after replotting on semilog graph paper. This determination was performed on six of the curves by ten investigators and five of these were asked to repeat their estimation after an interval of one week. Three of the investigators (C. E., V. T., and S. C.) were technicians in the Cardiology Department of the General Infirmary at Leeds and had much experience in calculating cardiac outputs and vascular volumes from dye dilution curves. The other investigators were either members of the academic or technical staff of the Department of Anaesthesia, University of Leeds.

Those curves that decayed rapidly towards zero were replotted on linear coordinates after the elimination of recirculation. The area under the total curve was then determined by use of both the planimeter and by numerical integration. Finally, an empirical method of estimating the area under the curve was applied as described by Warner and Wood. In this method the uncorrected dye curve is approximated by a triangle the apex of which coincides with the point of maximum dye concentration. Its sides are respectively a line between the apex and the point of initial appearance of the dye, and a line from the apex closely following the downslope before recirculation, and produced to meet the X axis. The required area is then taken to be an empirical factor (found by Warner and Wood to be 1.324) times the area of the approximating triangle.

**Results**

The results of measurements made on the foreparts of the 12 curves, i.e., up to the beginning of the exponentially falling region, are given in table 1. The use of a simple summation procedure systematically overestimated the area, but, when the ordinates were spaced at one-second intervals, there was little difference between the results from the trapezoid rule and from Simpson's rule. Similar results were obtained when estimating the integral \( \int t c(t) \, dt \). The planimeter gave areas in good agreement with Simpson's rule.

In the nine curves in which decay was rapid enough to make the estimations not too laborious, there was little difference between the various numerical integration procedures.
used to estimate the areas under the curves after the elimination of recirculation (table 2). The formula of Warner and Wood overestimated the area systematically.

Considerable variability was found in the estimates of the decay constants made by the ten investigators (table 3). The coefficient of variation ranged from 1.2% to 7.8%. Less variability was found between the duplicate estimates made by various workers on two occasions (table 4).

**Discussion**

It is clear that the errors which may occur in the processing of dye dilution curves are of two types. These are, first, the errors which arise because of difficulty in estimation of the decay constant, and second, the errors due to the use of an inappropriate integration formula.

It has been demonstrated that estimations of the decay constant of that part of the curves which is decaying exponentially vary both from person to person, and also, to a lesser extent, from time to time in the same person. The simplest way of investigating the probable errors due to this cause is to take a likely range of values of the decay constant, i.e., mean ± 2 standard deviations, and to work out the effect which these variations would have on the calculated cardiac output and vascular volume. This has been done in table 5. It is seen that in the worst case (curve 6) an error of almost 10% in the calculated

**TABLE 2**

Values of the Integral \( \int f(t) \, dt \) for Nine Dye Dilution Curves (Replotted to Eliminate the Effect of Recirculation) Estimated by Various Methods

<table>
<thead>
<tr>
<th>Curve</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>12</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple summation</td>
<td>84.5</td>
<td>32.7</td>
<td>64.8</td>
<td>61.3</td>
<td>40.9</td>
<td>46.0</td>
<td>31.4</td>
<td>64.3</td>
<td>63.6</td>
<td>54.37</td>
<td></td>
</tr>
<tr>
<td>Trapezoid rule</td>
<td>84.5</td>
<td>32.7</td>
<td>64.8</td>
<td>61.3</td>
<td>40.9</td>
<td>46.0</td>
<td>31.4</td>
<td>64.3</td>
<td>63.6</td>
<td>54.37</td>
<td></td>
</tr>
<tr>
<td>Simpson's rule</td>
<td>84.4</td>
<td>32.6</td>
<td>64.3</td>
<td>61.5</td>
<td>40.9</td>
<td>45.9</td>
<td>31.4</td>
<td>64.4</td>
<td>63.8</td>
<td>54.27</td>
<td></td>
</tr>
<tr>
<td>Planimeter method of Warner and Wood</td>
<td>87.2</td>
<td>33.8</td>
<td>69.0</td>
<td>62.9</td>
<td>48.4</td>
<td>48.7</td>
<td>34.0</td>
<td>68.0</td>
<td>67.3</td>
<td>57.70</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3**

Estimations (by 10 Investigators) of Decay Constants of Six Dye Dilution Curves

<table>
<thead>
<tr>
<th>Curve</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.K.</td>
<td>.147</td>
<td>.167</td>
<td>.184</td>
<td>.296</td>
<td>.0927</td>
<td>.0736</td>
</tr>
<tr>
<td>C.E.</td>
<td>.126</td>
<td>.153</td>
<td>.162</td>
<td>.298</td>
<td>.0942</td>
<td>.0643</td>
</tr>
<tr>
<td>V.T.</td>
<td>.133</td>
<td>.147</td>
<td>.157</td>
<td>.304</td>
<td>.0945</td>
<td>.0689</td>
</tr>
<tr>
<td>S.E.</td>
<td>.141</td>
<td>.159</td>
<td>.165</td>
<td>.306</td>
<td>.0932</td>
<td>.0692</td>
</tr>
<tr>
<td>J.B.</td>
<td>.144</td>
<td>.163</td>
<td>.158</td>
<td>.296</td>
<td>.0936</td>
<td>.0706</td>
</tr>
<tr>
<td>C.R.</td>
<td>.135</td>
<td>.156</td>
<td>.174</td>
<td>.328</td>
<td>.0945</td>
<td>.0743</td>
</tr>
<tr>
<td>B.G.</td>
<td>.132</td>
<td>.144</td>
<td>.158</td>
<td>.274</td>
<td>.0908</td>
<td>.0618</td>
</tr>
<tr>
<td>J.P.</td>
<td>.139</td>
<td>.157</td>
<td>.169</td>
<td>.276</td>
<td>.0940</td>
<td>.0756</td>
</tr>
<tr>
<td>R.G.</td>
<td>.121</td>
<td>.151</td>
<td>.174</td>
<td>.332</td>
<td>.0940</td>
<td>.0747</td>
</tr>
<tr>
<td>M.H.</td>
<td>.138</td>
<td>.154</td>
<td>.169</td>
<td>.314</td>
<td>.0931</td>
<td>.0806</td>
</tr>
<tr>
<td>Mean</td>
<td>.136</td>
<td>.155</td>
<td>.167</td>
<td>.302</td>
<td>.0936</td>
<td>.0716</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>.008</td>
<td>.007</td>
<td>.008</td>
<td>.019</td>
<td>.011</td>
<td>.0056</td>
</tr>
<tr>
<td>Coefficient of variation, %</td>
<td>5.9</td>
<td>4.5</td>
<td>4.8</td>
<td>6.3</td>
<td>1.2</td>
<td>7.8</td>
</tr>
</tbody>
</table>
cardiac output is produced. The estimation of the decay constant of curve 6 was particularly difficult because recirculation occurred early (fig. 2). It is usual to take precautions against this, but sometimes, for example, if the circulation is sluggish, recirculation will occur early on the down-limb despite these precautions. Even with good quality curves such as curve 4 (fig. 3) an error of up to 5% in the calculated cardiac output is possible.

The errors in the calculation of vascular volume are smaller because errors in the determination of decay constant tend to affect cardiac output and mean transit time in opposite directions. In the case of curves 4 and 6 this error is approximately 4%. It is likely that errors due to faulty estimation of the decay constant are the cause of some of the variability which is commonly reported in studies of the accuracy of the dye dilution technique. A recent paper on this topic is that of Hanson and Tabakin1 who measured the arterial dye concentration by two dye densitometers arranged in series. The variability between the cardiac outputs from the two units was of the order of 13% (95% confidence limits), and it is suggested here that this was partly, but not entirely, due to difficulties in processing the dye curves.

The question which must be considered at this stage is whether the accuracy would be improved if the decay constant were determined by some curve fitting technique. It is, of course, a simple matter to fit the best straight line in the least squares sense to any given set of points. However, before this can be done, the appropriate points must be chosen. In curves resembling those shown in figure 2 this is not easy because the...
exponential down-slope of the curve both starts and finishes gradually. Judgement is required in deciding just which points should be included in the curve-fitting technique. Despite this, it is likely that the accuracy would be increased by using a curve-fitting technique instead of estimating the slope by eye. It is unlikely, however, that the increased accuracy would justify the considerably increased labour involved.

The other errors which must be considered are those occasioned by the use of an inappropriate integration formula. When the ordinates are measured at one-second intervals, there is little difference in the areas obtained by means of the trapezoid rule and Simpson's rule. However, if Simpson's rule is used, it is possible to space the ordinates more widely and still achieve an accuracy comparable to that given by the trapezoid rule with ordinates spaced at one-second intervals. For example, if Simpson's rule is applied to the whole of curve 1, with ordinates spaced at three-second intervals, the calculated area is 84.48 which is the same as the value given by the trapezoid rule with one-second intervals. Since the dye curves with no recirculation come down to zero at both ends, the value given by the trapezoid rule is the same as that given by a simple summation.

A commonly adopted procedure is to estimate the forepart of the curve numerically and the latter part analytically. When this procedure is adopted it is seen that appreciable errors are introduced by the use of a summation instead of an integration formula. This is the case because the end ordinate is not zero. In the curves under consideration the systematic error introduced in the calculated cardiac output ranged from approximately -1.4 to -5.1%. As before there is little difference between areas given by the trapezoid rule and by Simpson's rule, although if the latter were used, then less ordinates could be used with little loss of accuracy. When estimating the integral \( \int t \ c(t) \ dt \) for the foreparts of the curves similar errors occur if a simple summation is used, but again there is little

Circulation Research, Vol. XVIII, May 1966
difference between the results from Simpson's rule and those from the trapezoid rule. The integral \( \int t c(t) \, dt \) was not estimated numerically for the latter parts of the curves because of the labour involved but similar results to those quoted above would have been obtained.

It must be emphasized that, unlike the errors due to difficulty in the estimation of the decay constant, the errors just described are avoidable and arise only from the inappropriate use of simple summation as a method of integration. For all practical purposes the trapezoid rule is sufficiently accurate to eliminate them.

The results of planimetry show that for clinical use this method of measuring the areas is accurate, but for research purposes, it is probably better to use the trapezoid formula. The formula proposed by Warner and Wood systematically overestimated the area under the curve. This discrepancy may have been due to faulty construction of the triangle but clearly the use of this formula is likely to cause considerable error and is probably best avoided if accurate results are required.

We have so far been considering ways of processing dye curves by hand because this is still the method which is used in most centers. However, digital computers and analogue-to-digital converters are becoming more available for the processing of medical data, so that in the future the analysis of dye curves by digital computer may become the rule rather than the exception. In addition, special purpose analogue computers such as those described by Hara and Bellville, and Moody et al. are rapidly being developed for this purpose. It may well be that the use of computers will lead to increased accuracy in the calculation of cardiac output from dye dilution curves, but it should be emphasized that judgment will still be required in programming them to perform the most suitable calculations on a wide range of curves.

**Summary**

Errors of two kinds occur in the processing of dye dilution curves:

1) Individual estimates of the decay constant of a dye curve are subject to random errors causing a variability of up to 10% in the calculated cardiac output, and of up to 4% in the estimated vascular volume.

2) The use of an inappropriate numerical integration formula can cause an additional error of up to 5% in the calculated cardiac output. This may be avoided by using either the trapezoid rule or Simpson's rule. The planimeter measures areas with sufficient accuracy for routine determination of cardiac output.

**References**

Errors in the Processing of Dye Dilution Curves
G. Richard Kelman

Circ Res. 1966;18:543-549
doi: 10.1161/01.RES.18.5.543

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/18/5/543

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/