A New Method Utilizing Indicator-Dilution Technics for Estimation of Left-to-Right Shunts in Infants

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In infants the short circulatory pathways result in rapid pulmonary and systemic circulation times. So rapid is the transit of blood, that in the presence of a left-to-right shunt, an indicator injected into the right heart arrives a second time at an arterial sampling site prior to the inscription of the concentration peak. This then results in the lack of discrimination of left-to-right shunts and also completely negates the usual method of the Stewart Hamilton calculation of cardiac outputs.

During the course of an investigation of the cardiovascular hemodynamics in a group of normal neonates, the authors found that the usual method for calculating left-to-right shunts by indicator-dilution contour yielded erroneously high magnitudes. The formula to be proposed here is based on a modification of a right-to-left shunt formula, applied to left heart injections of indicator. This new formula compares favorably to estimates of left-to-right shunts obtained by oximetry.

Materials and Methods

All the patients included in this report underwent cardiac catheterization for diagnostic purposes. Included are 11 infants ranging from 11 days to 10 months in age and from 2.4 to 7.2 Kg. in weight. Each of these children had only a left-to-right shunt that included two patent ductus arteriosus, six ventricular septal defects, and three atrial septal defects.

The indicator used throughout this study was indocyanine green, (Cardiogreen). Systemic arterial blood was withdrawn by means of a Harvard constant rate infusion-withdrawal pump at rates of 16 or 36 mL/min. through a Waters XC250 A densitometer. Calvanometer deflections were recorded on a Minneapolis Honeywell Visicorder, model 1108. Multiple intracardiac and great-veesl blood samples were drawn in every case through a Waters XC-50B cuvette oximeter. The cuvette oximeter was calibrated for each patient by two or more simultaneous measurements of oxygen determined by the Van Slyke-Neill method.

Left-to-right shunts were calculated by three methods for each patient: (1) oxygen saturations and the formula pulmonary artery-mixed venous/systemic artery-mixed venous, (2) indicator-dilution curves following injections of dye into the right heart and Carter's formula (fig. 1), and (3) our newly devised formula, which utilizes information obtained from both right and left heart injections of dye. This formula encompasses two areas (fig. 2). Area 1 of the dye curve is assumed to be proportional to the amount of blood flowing in the normal circulatory pathway and in turn is proportional to the product of peak concentration (Cn) and build-up time (Tn). Area 2 similarly represents the left-to-right shunt pathway and is proportional to the product of peak concentration of the shunt (Cp) and pulmonary circulation time (PCT). This latter value is obtained from the difference in appearance times of sequential right and left heart injections. Obviously, the presence of an additional right-to-left shunt invalidates this procedure. The magnitude of the left-to-right shunt is obtained by dividing area 2 by the sum of area 1 plus area 2, the result being expressed as per cent of pulmonary blood flow.

Concentrations are expressed in mg./L. and time is in seconds. If a densitometer with a linear calibration curve is employed, centimeters of galvanometer deflection may be employed in lieu of the actual concentrations. Since this expression employs a ratio of concentrations, the calibration constant will cancel with a linear calibration curve.

Results

A typical dye curve obtained following in-
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Figure 1

Indicator-dilution curve obtained following injections into superior vena cava and sampling in the root of aorta of a 10-month-old, 7.2 Kg. child with a surgically proven patent ductus arteriosus. The arrow, in this and subsequent figures, refers to the mid-point of the injection of dye, corrected for transit of arterial blood through the sampling system. The formula proposed by Carter et al. for dilution curves recorded at the radial artery and validated by them for right-sided injections in older children and adults is

\[
141 \times \frac{C(2BT)}{C(BT)} - 42 \\
135 \times \frac{C(3BT)}{C(BT)} - 14
\]

where \( C \) refers to concentration after each multiple of the build-up time (BT). The values obtained from these two calculations are averaged and express the per cent of pulmonary blood flow contributed by the left-to-right shunt.

Injection of dye into the right atrium of an infant with a left-to-right shunt is shown in figure 1. The curve in figure 2 recorded from the same infant following left atrial injection. The latter curve shows a definite break on the down slope due to recirculation of shunted dyed blood through the lungs. As noted on these figures, calculations based on right heart injection overestimated the degree of left-to-right shunt, while calculations with the new formula based on left atrial injection showed excellent agreement with that calculated from oximetric data.

The estimated left-to-right shunt after right heart injection of dye in 11 infants as compared to oximetry is shown in figure 3. It is obvious that a large error, generally an overestimation, in the magnitude of the left-to-right shunt results. Less than half (17 of 36) of the values are within 20 per cent of the oximetric calculations.

The results of left heart injections in these 11 infants are shown in figure 4. All of these values are within 20 per cent of the oximetric calculations.

**Figure 2**

Indicator-dilution curve recorded after left atrial injection in the same patient as that of figure 1. The catheter was placed into the left atrium through the foramen ovale by an inferior vena caval approach. Note the shorter appearance time. Our proposed method for calculating left-to-right shunts from left heart dye curves is as follows:

\[
L \rightarrow R \text{ shunt (as % P.B.F.)} = \frac{C_s(T_s - PCT)}{C_s(T_s - PCT) + C_nT_n}
\]

where \( C_n \) is the initial (normal) concentration peak in mg./L. (If the densitometer used has a linear calibration curve, centimeters of galvanometer deflection may be used instead of mg./L. for \( C_n \) and \( C_s \))

\( T_n \) is the time from the initial appearance of dye to \( C_n \)

\( C_s \) is the second (shunt) concentration peak

\( T_s \) is the time from initial appearance of dye to \( C_s \)

PCT is the pulmonary circulation time, estimated in turn by the difference in appearance times of dye curves obtained following right heart and left heart injections of dye. It is preferable to minimize the time between the performance of such a pair of dye curves.
Discussion

The original method of Carter and co-workers, based on the rate of disappearance of dye from the circulation, was found to be inapplicable to infants for reasons to follow in the discussion. The empirical constants in Carter's formula were obtained from right heart injections with arterial sampling. The subjects for this investigation ranged from 3 to 56 years of age. Generally excellent agreement with oximetric calculations were obtained when the left-to-right shunt exceeded 35 per cent of pulmonary blood flow. Below that value the disappearance ratio method becomes increasingly inaccurate and frequently left-to-right shunts of this magnitude cannot be distinguished from normal dye-dilution curves.

In infants and small children, the time of appearance of dye shunted through pulmonary flow pathways is recorded prior to the inscription of the concentration peak. This results in a high disappearance ratio and an erroneously high estimation of the magnitude of the shunt. Figure 5 illustrates this point further. The initial portions of curves obtained after injection into the right and left atria in a normal newborn are shown as solid lines. Then, knowing the difference in appearance times between the pair of curves, the short dotted line was added to indicate the esti-
mated time shunted dyed blood lags behind dyed blood flowing in normal circulatory pathways. This shows that after right atrial injection, shunted dye (the short solid lines) appears on the upstroke of the recorded dye curve, while after left atrial injection shunted dye appears after peak concentration is reached. In 14 neonates and eight infants studied to date, pulmonary circulation time was always greater than time from initial appearance of dye to peak concentration following left heart injection. Pulmonary circulation time was always less than time from initial appearance to peak concentration after right atrial injection.

The formula developed by Carter et al. was not proposed for and has never been validated for left-heart injections. Dye curves obtained following right-heart injection generally show a distinct notch following the inscription of peak concentrations when a left-to-right shunt is present (fig. 2). Our initial attempts to apply this formula to left heart injections frequently resulted in the calculation of two grossly disparate values, with the first value as much as 50 per cent lower than the second. The use of an average value obtained from two such disparate calculations is of doubtful validity, and an unwarranted extension (on our part) of Carter’s intentions.

The proposed formula involves the estimation of pulmonary circulation time in order to obtain the appearance time for shunted dye. After entering the left atrium, the shunted blood re-enters the right side, passes through the lungs, and then goes back to the left atrium. The time taken to travel from left atrium to left atrium is the exact amount of time by which shunted blood lags behind the initial normal dyed blood. Since the pathways are almost identical, this is essentially equal to right atrium-to-left atrium time. Thus, pulmonary circulation time can be estimated by the difference in appearance times of dye injected into the right atrium and dye injected into the left atrium, provided always that no right-to-left shunt is present. Only a small error at the most is introduced by substituting a ventricular site for one or both of these injections.*

In infants, accuracy in the determination of these injection times is of considerable importance. In a group of 14 neonates, the averaged corrected time of appearance for dye injected into the right atrium and sampled in the abdominal aorta was 2.2 seconds. This time interval decreased to 1.0 seconds for dye injected into the left atrium. Right atrial-to-left atrial circulation time, thus averaged 1.2 seconds. A dye syringe holder with provision for electrical timing of the injection eliminates the need for a manual injection signal. For neonates and small infants, the catheter injection system should also be primed by filling it with the indicator solution and then an additional exact amount of indicator to be injected. Using this combination of dye displacement and electrical timing, we are able to obtain reproducibility of appearance times within 0.1 second.

Indicator-dilution techinics are extremely valuable for small infants. The difficulties of oximetric calculations are further compounded by the absence of a truly steady state. This renders it difficult to obtain a series of blood samples for oximetric calculations without a change in the status of the infant. In contrast, the two dye curves necessary for the left-to-right shunt formula calculation described here can be obtained very rapidly, usually in less than 2 minutes. Since the oximetric method of calculations involves a subtraction, even relatively small errors in single oximetric determinations of oxygen saturation become greatly magnified when applied to the smaller differences obtained from the formula. Furthermore, this oximetric calculation fails completely at levels of left-to-right shunt below approximately 20 per cent of pulmonary blood flow.

This method was also tested in seven

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*We have injected dye into both left ventricle and left atrium in each of two infants without a detectable difference in appearance times, using the electrical timing of injection and dye-displacement techinics explained in the next paragraph.
older patients ranging from 28 months to 39 years in age. Essentially similar results were noted, namely, eight of nine left heart injections were within 20 per cent of the value established by oximetry (fig. 4). These results are included to demonstrate that this formula, while necessary in infants, also works for older and larger subjects.

Oximetry did not detect one of the shunts in this group. In this instance, dye was injected into the left ventricle and sampled simultaneously through two densitometers attached to catheters in the main pulmonary artery and the femoral artery. For this small shunt, calculated at only 16 per cent of pulmonary blood flow, the dye curves obtained following right-sided injection of dye were normal. Injection into the left ventricle showed an obvious second concentration peak similar to that illustrated in figure 2. The left-to-right shunt calculated by the proposed formula was 25 per cent of the pulmonary blood flow.

The catheterization of this patient was interesting from yet another facet. All of the clinical and catheterization data were consistent with a small ventricular septal defect, except for one pair of dye curves obtained following injection of dye into the left ventricle with simultaneous sampling from the main pulmonary artery and the femoral artery. In this case, the shunt calculated by our method was 44 per cent of pulmonary blood flow and 47 per cent of pulmonary blood flow as calculated from the dye curve pairs. It is probable that these values were obtained with the tip of the injection catheter pointing either toward or actually within the limits of the ventricular septal defect. This illustrates the value of multiple injection sites. An upstream injection site, e.g., pulmonary vein or left atrium, should be used whenever possible to provide at least a minimal opportunity for mixing of dye and blood. In common with all indicator-dilution techniques, mixing of dye and blood is a necessary assumption. Less opportunity for this exists when the injection site is distal to the pulmonary circulation.8,9 It is probable that this method will give erroneous values for left-to-right shunts through an atrial septal defect, even when averaged for injections into both right and left pulmonary veins.

Summary

The short circulatory pathways of infants cause rapid systemic and pulmonary circulation times. So rapid are they that the usual methods for calculating left-to-right shunts frequently yield a considerable overestimation. A new formula was described for use with injections into the left heart and arterial sampling. This formula applied to 11 infants and 7 older patients showed a significantly better correlation with oximetric calculations than did the right heart injections. This method also will reveal the presence of a left-to-right shunt that is of insufficient magnitude to distort dye curves obtained following right heart injections.

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References

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