A Simplified Method for Quantitating Left-to-Right Shunts from Arterial Dilution Curves

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SUMMARY
This report presents a new, simple and reliable method of quantitating left-to-right shunts from arterial dilution curves. When indicator (e.g., indocyanine green) is injected centrally (right ventricle or pulmonary artery) and blood is withdrawn rapidly from either the aorta or other central systemic artery, in the presence of a left-to-right shunt the recorded indicator-dilution curve usually shows two discrete peaks: \( P_1 \) of pulmonary blood flow and \( P_2 \) of shunt flow. The formula, \( P_2/P_1 \times 100 \) has been found to reliably estimate the magnitude of the shunt expressed as percent of pulmonary blood flow. Experimental and clinical data demonstrate that this method is accurate in quantitating shunts from such curves.

Additional Indexing Words:
Indicator dilution curves
Indocyanine green dye
Dye curves
Experimental left-to-right shunt
Congenital heart disease

In 1960, Carter et al.\(^1\) derived an empirical formula for calculating left-to-right shunts from arterial dilution curves. Their method is based on the rate of disappearance of the indicator at specific times following its point of maximum concentration. Magnitude of the left-to-right shunt is expressed as percent of pulmonary blood flow. Since its introduction the Carter formula has been commonly used for calculating catheterization data.\(^2\)-\(^5\)

In the presence of a left-to-right shunt over 20% of pulmonary blood flow the Carter formula gives consistent and satisfactory results when applied to relatively slowly recorded curves with continually decreasing disappearance slopes. Clinical experience, on the other hand, has shown it to be considerably less accurate when the curves are sharply defined. This is particularly true when circulation times are rapid, when injection and sampling sites are close together (as in pulmonary artery to aorta dye curves) and when blood is rapidly withdrawn from the sampling site. In these situations the initial disappearance slope is usually interrupted by a second build-up and peak, representing recirculating shunt flow. Therefore, an experimental investigation was carried out to seek a more applicable method of quantitating left-to-right shunts from such curves.

Materials and Methods
Eight adult mongrel dogs, weighing between 20 and 24 kg were used. Each animal was anesthetized with intravenous sodium pentobarbital, respiration being controlled by means of an endotracheal tube connected to a mechanical respirator with water-positive pressure in the expiratory phase. Catheters were introduced via the femoral vessels and placed, under fluoroscopic control, in the arch of the aorta, pulmonary artery and inferior vena cava. Pressures were recorded with calibrated Statham strain gauges. The heart was exposed through a midline thoracotomy, the root of the aorta dissected free and purse string sutures placed at the apex of the left ventricle and around the base of the right atrial appendage. Immediately after 6 cc of xylocaine were given intravenously, as an antiarrhythmic agent, an 8 mm diameter polyethylene tube was inserted into the left ventricle through a stab wound at the apex, and secured by the previously placed sutures. A similar tube was inserted and secured in the right atrial appendage. The tubes were then connected to each other through an extracorporeal flowmeter probe (Electromagnetic Probe Co-model 300) for constant measurement of the left ventricle-right atrium shunt flow. The magnitude of the shunt flow was controlled by a screw clamp on the connecting tube. A proper sized flowmeter probe (Model 500) was also placed around the ascending
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All flowmeter probes had an accurate and linear response during in vitro calibration with flows ranging from 0.5 to 3 L/min. The extracorporeal and aortic probes were connected to a Carolina Medical Electronics Square-Wave Electromagnetic Flowmeter (Model 321) through an SB-324 switch box. In this way both the shunt and systemic blood flows could be recorded in rapid sequence. Mechanical zero was easily obtained in the extracorporeal probe by distal clamping of the connecting tube. Since cross-clamping of the aorta resulted in rapid deterioration of the animal, this was done only at the beginning; thereafter the diastolic level of aortic pulsatile flow was used as a zero reference. Both zeros were frequently checked during the study, particularly after each increment of shunt flow. Electrical zeros were checked before each dye curve. Pulmonary blood flow was considered to be equal to systemic plus shunt flow and the percent shunt as the ratio of shunt flow to pulmonary blood flow.

Indocyanine green dye was mixed at a concentration of 1 mg/L. Calibration of a Waters X-C100A densitometer was performed in each animal using four blood samples containing different known concentrations of dye in addition to blood with no added dye. After the pulmonary artery catheter was fully charged with green dye, injections were made by displacement using a specially designed syringe that electronically recorded the injection time. Blood from the aortic sampling site was withdrawn through the previously calibrated densitometer by a Harvard pump at a constant rate of 38.2 ml/min. All curves were recorded on a Honeywell Visicorder (Model 1108) at a paper speed of 5 mm/sec. The amount of dye injected was controlled so that the maximum concentration recorded during the curve was within the linear response of the calibrated densitometer.

Systemic and shunt flows measured by the flowmeters were immediately recorded before each dye curve. A total of 20 dye curves were made with the shunt completely closed and 111 with shunts ranging from 15% to over 60% of pulmonary blood flow.

Results

The Carter formula was applied to all shunt curves. The calculated left-to-right shunt, expressed as percent of pulmonary blood flow, was then plotted against that measured by the flowmeters. On the average, the Carter formula underestimated the left-to-right shunt with considerable scatter at all magnitudes of shunt as determined by flowmeter readings (fig. 2).

It soon became apparent that all shunt curves had a second peak prior to appearance of systemic recirculation (fig. 3). Since the indicator was injected into the pulmonary artery, the triangular area determined by the first peak \( P_1 \) and the build-up time represented pulmonary blood flow. The point of maximal concentration of the second peak \( P_2 \), on the other hand, was considered to reflect predominantly shunt flow.

Since the appearance time of the second (shunt) peak could not be determined with certainty and because there is always some overlapping of the two areas, the ratio of the height of the peaks \( P_2/P_1 \times 100 \) was considered as a potential estimator of shunt magnitude. When compared with the flowmeter readings, \( P_2/P_1 \) gave more accurate estimates with considerably less variability than the Carter formula (fig. 4).

An analysis of covariance linear model was used as the basic statistical tool. For each dog the regression of estimated shunt was computed. The between-dog variability was seen to be small when compared to

**Figure 1**

Schematic representation of the experimental model with the surgically created external left-to-right shunt and flowmeter probes. LV: left ventricle; RA: right atrium; Ao: aorta.

**Figure 2**

Correlation of the magnitude of the experimental left-to-right shunt (expressed as percent of the pulmonary blood flow) measured by the flowmeters with that calculated by the Carter formula. Note that this method generally underestimates the shunt size with only 33% of the values falling within ±20% of the line of identity (solid line).
within-dog variability. This was true for both the Carter method and the $P_2/P_1$ method. The data from individual dogs were subsequently pooled to calculate a single regression line for the Carter method and a single regression line for the $P_2/P_1$ method. The slopes of these two regression lines are essentially the same (.71 vs .73). However, the Carter method was found to be significantly more variable ($P < .01$, F-test). This results in a greater correlation for the $P_2/P_1$ method compared to the Carter method (.84 vs .71) (fig. 5). The BMD $\times$ 63 - Multivariate General Linear Hypothesis Program\(^8\) was used to carry out computations.

Clinical Study

The experimentally derived formula was then applied in a retrospective analysis of 122 patients (ages 3 months to 16 years) with isolated ventricular septal defects. Included in the study were all patients in our series who had adequate oximetry data and who had arterial indicator dilution curves, with injection of dye in the pulmonary artery performed during their cardiac catheterization. The Carter formula was applied to each curve and the calculated value of the left-to-right shunt compared with that determined by oximetry (by the Van Slyke analysis and/or spectrophotometric method). As in the dog experiment, the Carter formula underestimated the shunt size, particularly those between 30% and 60% of pulmonary blood flow (fig. 6). In 107 of these patients (88%) the curves showed a discrete second peak due to the shunt. Shunt calculation by the formula $P_2/P_1$ was compared with that measured by oximetry (fig. 7). $P_2/P_1$ gave a much better correlation at all magnitudes of shunts than did the Carter formula.

Regression equations relating the Carter and $P_2/P_1$ estimates to oximetry readings were obtained (fig. 8) showing that the $P_2/P_1$ method gives more accurate estimates with a correlation coefficient of 0.90 versus 0.82 for the Carter formula.

Regression equations relating the Carter (top) and $P_2/P_1$ (bottom) estimates with flowmeter measured shunts ranging from 30% to 65% of the pulmonary blood flow. The interrupted lines indicate two standard deviations from the regression line (heavy solid line). Note that on the average, the $P_2/P_1$ method gives more accurate estimates with less variability than the Carter formula.
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Comparison between the estimated shunt by the Carter formula and that obtained by oximetry in 122 patients with isolated ventricular septal defects (VSD). Only 38% of the values are within ±20% of the line of identity (solid line). As in the dog experiment, the Carter formula underestimated the shunt size, particularly those between 30 and 60% of the pulmonary blood flow.

Discussion

In patients with significant left-to-right shunts, arterial dilution curves show a characteristic distortion of the downslope, due to early recirculation of indicator through the shunt. Twenty years ago, Broadbent and Wood9 demonstrated a positive correlation between the degree of distortion and the size of the left-to-right shunt. The magnitude of the shunt was estimated using the ratio of the disappearance time to the build-up time. It was soon realized that, while the method was useful for dilution curves recorded after injection of indicator into a peripheral vein, it could not be applied to curves obtained from the pulmonary artery. Thus, Carter and co-workers1 developed the now widely-used formula to be applied when indicator is injected into a more central site (pulmonary artery, right ventricle or a vena cava). In deriving this formula all curves were recorded from an indwelling 20 gauge needle placed in the radial artery. This distal sampling site together with the slower rate of withdrawal of blood through the curvette oximeter explains the smooth disappearance slope observed in their sample curve. In contrast, during routine cardiac catheterization, dye curves often are recorded from more central arteries (e.g., aorta) using larger catheters that allow rapid withdrawal rates. As a consequence the curves are more sharply defined.

In our experience, the Carter formula gives acceptable results when applied to curves with a relatively slow and continually decreasing disappearance slope, as in the presence of large shunts or when the dye is injected into either vena cava or the right atrium.

Comparison between the quantitation of the left-to-right shunt by oximetry and the $P_2/P_1$ ratio in 107 patients with isolated ventricular septal defects who had a double peak in their pulmonary artery dye curves. Note an excellent correlation at all magnitudes of shunt.

Regression equations relating the Carter (top) and $P_2/P_1$ (bottom) estimates to oximetry calculated shunts in patients with ventricular septal defects. The results indicate that the $P_2/P_1$ method gives much more accurate estimates with a variability less than half that of the Carter formula.

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When the dye is injected into the right ventricle or pulmonary artery, particularly in patients with moderate shunts, the formula is less accurate and the results correlate less well with shunt calculation by other methods. The most likely reason for this failure is that in these sharper curves the build-up time is shorter and the disappearance rate more rapid. The shunt then appears later, relative to the primary curve, resulting in a discrete second peak rather than simply a change in rate of the disappearance of the primary peak. The combination of a more normal primary curve and a discrete shunt curve invalidates the Carter formula. This is not surprising since the Carter formula was derived from curves in which the shunt recirculation blends with the disappearance slope of the primary curve and thus it should not be expected to apply to a separate set of circumstances. In double peak curves we believe that the area of the first peak represents pulmonary blood flow while that of the second peak reflects shunt flow. After considering several alternatives and the practical difficulties in separately measuring the two triangular areas, it was decided to construct a ratio between the height of the peaks. This experimental and clinical investigation demonstrates that this ratio, $P_2/P_1 \times 100$, is a simple and accurate method for quantitating left-to-right shunts from such curves.

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