Pulse Densitometer Indocyanine Green Dilution Curves: A Simple Applicable and Accurate Method for Determination of Cardiac Shunts

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ABSTRACT

Objective. Adequate hemodynamic evaluation is crucial in the management of patients with congenital heart disease. Although non-invasive diagnostic tools have reduced the need for invasive procedures, cardiac catheterization is still mandatory for absolute quantification of pressures, flows and vascular resistances in selected patients. We therefore investigated the feasibility of a new technique, non-invasive pulse densitometry (PD) in patients with intracardiac shunts and compared its results with the established standards: cuvette densitometry (CD) and oximetry (OX).


Outcome measure. In 12 patients with intracardiac shunt, dye dilution curves, using both pulse and cuvette densitometry, were recorded and oximetry was performed. Left-to-right shunt expressed as percentage of pulmonary blood flow Qp, was calculated from dye dilution and oximetry. In 4 patients with atrial septal defect, dye dilution curves were also recorded after closure of the defect with a device.

Results. The mean difference ± SD between the shunt derived from PD and CD was 2.8 ± 10.0% of Qp, 95% confidence interval -2.5 to 8.2. (Shunt-PD vs. Shunt-CD was 32.3 ± 23.9% vs. 29.5 ± 23.9% of Qp resp., n = 16). The mean difference ± SD between the shunt derived from PD and OX was 0.8 ± 9.8% of Qp, 95% confidence interval -5.4 to 7.0 (Shunt-PD vs. Shunt-OX was 41.5 ± 20.3% vs. 40.7 ± 19.7% of Qp resp., n = 12).

Conclusion. Transcutaneous recording of dye dilution curves with a pulse dye densitometer allows easy and accurate quantification of intracardiac left-to-right shunt flows over a wide range in both children and adults with congenital heart diseases.

Key Words. Intracardiac Shunt; Blood Flow; Cuvette Densitometry; Oximetry; Congenital Heart Disease

Introduction

In congenital heart disease, hemodynamic variables, such as cardiac output, the presence and magnitude of cardiac shunts, pulmonary and systemic pressures and resistances are often key factors in diagnosis, treatment, and prognosis of individual patients; in particular, in patients with pulmonary hypertension or complex lesions like univentricular hearts, in whom the degree of pulmonary vascular resistance may guide the choice of treatment.

Noninvasive methods to determine these variables, such as echocardiography and cardiac magnetic resonance imaging (MRI), have improved dramatically in the recent years and certainly have reduced the need for invasive procedures in these patients. Echocardiography can reliably demonstrate the presence and direction of intracardiac shunts; however, it cannot reliably quantitate blood flows and shunts, required for the calculation of vascular resistances. MRI has been suggested to adequately quantitate intracardiac (but not extracardiac) shunts and to estimate cardiac output, but fails to incorporate vascular pressures, required for calculation of resistances. Therefore invasive procedures, such as cardiac catheterization, keep having its place in the
functional evaluation of selected patients with congenital heart disease.

However, until today, accurate blood flow measurements in the clinical setting and in invasive procedures remain problematic. Various invasive methods are in use to quantitate cardiac output and intracardiac shunts, and all have their specific practical and conceptual limitations. The direct Fick method may be regarded as the gold standard for blood flow measurement. However, accurate measurement of oxygen consumption is often deemed too complicated for clinical application and therefore an assumed oxygen consumption is frequently used in routine catheterization laboratories. Assuming oxygen consumption using predictive formulas, however, may result in errors, especially in patients with congenital heart disease.1-3 Further, the determination of mixed venous oxygen saturation in cases of pre-tricuspid shunt, and of mixed pulmonary arterial oxygen saturation in inter-arterial shunts, such as patent ductus arteriosus, may be subject to error.4,5 Therefore, the dye dilution method—developed some 100 years ago for the determination of cardiac output—has been for a long time the method of choice for invasive blood flow measurement and determination of shunts. A bolus of dye, in fact indocyanine green, is injected into the circulation (e.g., pulmonary artery) and sampled downstream (e.g., femoral artery) by continuous withdrawal through a densitometer cuvette. This leads to a concentration–time curve, normally characterized by a primary peak and a recirculation peak. In cases of left-to-right shunt, the curve additionally shows an early recirculation peak. Pulmonary blood flow and shunt can be calculated from this curve.6 Limitations of the indocyanine green dilution technique include: (1) the complexity and time-consuming nature of the procedure; (2) the need of temporary withdrawal of fairly large volumes of blood; and (3) problems in resterilization and availability of cuvettes. These mainly practical drawbacks have discouraged the use of the dye technique in the routine catheterization laboratory.7

Instead, the thermodilution technique, which uses temperature difference after injection of a bolus of a cold solution as an indicator, is currently the technique of choice for the invasive determination of cardiac output in patients. The thermodilution method has also been proposed for the determination of shunts,8 but “cold” proved to be an indicator with a high diffusibility, so that much is lost between injection and measurement.9 This is especially interfering with the measurement of shunts in which part of the indicator follows a longer pathway. Consequently, this technique cannot be used for quantification of shunts.

Recently, pulse dye densitometry has been introduced.10 This technique determines, after injection of a bolus of indocyanine green through a central or peripheral venous line, a dye concentration curve by pulse spectrophotometry using a finger probe or a nose probe. Thereby, this technique has eliminated the need of withdrawal of arterial blood and the use of a cuvette,11 while fully utilizing the favorable properties of indocyanine green. The suitability of pulse densitometry for measuring cardiac output and total blood volume after a single injection of indocyanine green has been demonstrated.10-12

We hypothesized that pulse dye densitometry is suitable to adequately quantitate shunts (and blood flows) in patients with shunts at various levels (pre-tricuspid, post-tricuspid, and/or arterial). Therefore, we studied 12 patients with congenital shunts and determined the magnitude of the shunt by pulse densitometry and compared the values with those determined by cuvette densitometry and by calculation of oxygen saturation measurements.

Material and Methods

Patients

Twelve patients with congenital left-to-right shunt, submitted for diagnostic or therapeutic cardiac catheterization, were included in this study after informed consent was obtained from the patient or the caregivers. Patient characteristics are shown in Table 1. All patients, except patient 11, were examined under general anesthesia.

Procedure

During right heart catheterization, intracardiac pressures and oxygen saturations were measured by standard methods. From the oxygen saturation data, the left-to-right shunt was calculated. Dye dilution curves were recorded after injection of 0.5–1.0 mL of a 5 mg/mL indocyanine green (Pulsion Medical Systems, Munich, Germany) solution in water. After the injection catheter had been filled with the dye solution, the injection was performed by displacement of the required volume of dye solution with an accurately scaled 1-mL syringe. The dye was injected into the pulmonary artery and/or right ventricle. Cuvette densitometer curves (Waters Instruments, Minne-
apolois, MN, USA*) were obtained by withdrawal of arterial blood at 35 mL/min. Pulse densitometer curves (DDG Analyzer, Nihon Kohden, Tokyo, Japan) were recorded simultaneously. The pulse densitometer is provided with a finger sensor and nose sensor. In this study, we only used the nose sensor. In our experience, it gives better fixation so that a more stable signal is obtained. Moreover, the curves obtained with the nose sensor show better resolution of main and secondary peaks.11 The nose sensor was placed at one of the nose wings. However, in patient 12 (Table 1) the nose sensor was placed at an ear lobe, because the nostrils were too small.

Calculations

The left-to-right shunt from the arterial dye dilution curve was calculated according to Mook and Zijlstra.13 This calculation is based on the assumption that, after a bolus injection of dye, the mixing of dye and blood is good enough to ensure that the amount of dye passing the defect is proportional to the shunt flow. The shunted amount of dye is considered to be a second injection into the right heart, resulting in the shunt part of the dye dilution curve. The normal part and the shunt part of the curve are separated by semi-logarithmic extrapolation of the descending limbs as shown in Figure 1. The areas of the two parts of the curve are determined by planimetry. The left-to-right shunt (Shunt) as a fraction (or percentage) of the pulmonary blood flow is then calculated by dividing the area under the shunt part (Ay) by the area under the normal part (An): Shunt = Ay/An (×100%). The ratio of pulmonary (Qp) and systemic blood flow (Qs) is then given by Qp/Qs = An/(An – Ay).

The normal peak in the pulse dye dilution curve was automatically extrapolated by the DDG analyzer; the normal peak of the cuvette dye dilution curve and the shunt peaks of both dilution curves were extrapolated by hand as shown in Figure 1. In calculating shunts from the dye dilution curves,

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Disease</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>49</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>20</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>43</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>25</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>14</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>5</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>6</td>
<td>ASD II</td>
<td>Closure with a device</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>5</td>
<td>ASD II + abnormal RPV</td>
<td>PDA + ASD</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>2</td>
<td>PDA + ASD</td>
<td>ASD</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>47</td>
<td>ASD</td>
<td>ASD</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>54</td>
<td>VSD</td>
<td>VSD</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>2</td>
<td>PDA</td>
<td>PDA</td>
</tr>
</tbody>
</table>

F, female; M, male; ASD II, atrial septal defect of the secundum type; AVSD, atrioventricular septal defect; PDA, persistent ductus arteriosus; abnormal RPV, abnormal drainage of a right pulmonary vein; VSD, ventricular septal defect.

*The cuvettes are no longer available from Waters Instruments Inc.

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Figure 1. Example of exponential (semi-logarithmic) extrapolation of a cuvette densitometer dye curve obtained in a 24-year-old man with a ventricular septal defect. Injection of 5 mg indocyanine green into the pulmonary artery. From peak concentration time t0, the down slope of the two peaks has been measured from the baseline and plotted on semi-logarithmic paper (lower panel). Points of the linearly extrapolated normal and shunt part of the curve have been replotted on the original curve, yielding two areas, An and Ay. An stands for the area under the normal peak and Ay for the area under the shunt peak, c stands for concentration; c n is the part of c corresponding to the dye that followed the normal pathway and c y is the part of c corresponding to the dye that followed the shunt pathway. (Modified from Mook and Zijlstra.13)
from the pulse densitometer as well as the cuvette densitometer, the mean value of two successive 
dilution curves was used. Shunts were also calculated using oximetric data (Shunt-OX). Shunt-
OX was calculated by dividing the difference of pulmonary artery oxygen saturation and mixed 
venous oxygen saturation by the difference of pulmonary vein or arterial oxygen saturation and the 
mixed venous oxygen saturation ($\times 100\%$).

**Statistics**

Data are expressed as: mean $\pm$ standard deviation (SD). The methods were compared according to 
Bland and Altman.

**Results**

Representative dye dilution curves, obtained in patient 11, are shown in Figure 2. The results of 
the shunt calculations from the dye dilution curves and the oxygen saturation data of the 12 patients 
are shown in Table 2. In four patients, dye dilution curves were also recorded after closure of the atrial 
septal defect with a device. In patient 6, the cuvette densitometer curve could not be extrapolated in 
the manner of Figure 1; the left-to-right shunt was calculated according to Carter et al.\textsuperscript{14}

![Figure 2. Two dye dilution curves recorded simultaneously after injection of 5 mg indocyanine green into the right pulmonary artery (patient 11). The upper panel shows the curve measured by withdrawing arterial blood from the right femoral artery through a densitometer cuvette. The lower panel shows the pulse densitometer curve measured at a nose wing, and recorded by the build-in printer, the x-axis calibrated in seconds. The main peak of the pulse densitometer curve has been extrapolated automatically. The shunt peak and both peaks of the cuvette densitometer curve have been extrapolated by hand. Note the better resolution of the two peaks by the pulse densitometer.](image_url)

The relationship between the shunts as measured with the pulse densitometer (Shunt-PD) and the shunts as measured with the cuvette densitometer (Shunt-CD) is shown in Figure 3A; 
Figure 3B shows a Bland-Altman plot of the individual differences. Mean $\pm$ SD of the difference 
between Shunt-PD and Shunt-CD was 2.8 $\pm$

\begin{table}[h]
\centering
\caption{Results}
\begin{tabular}{|c|c|c|c|c|}
\hline
Patient & Injection Site & Shunt-OX & Shunt-CD & Shunt-PD \\
\hline
1 & APC & 42 & 37 & 39 \\
2 & RV & — & 5 & 8 \\
3 & RV & 47 & 52 & 58 \\
4 & RV & 44 & 22 & 46 \\
5 & RV & 13 & 16 & 9 \\
6 & RV & 71 & 78 & 84 \\
7 & RV & 62 & 52 & 50 \\
8 & RV & 32 & 23 & 38 \\
9 & APC & 18 & 15 & 16 \\
10 & RV & 33 & 38 & 37 \\
11 & APD & 48 & 48 & 54 \\
12 & APC & 13 & 6 & 21 \\
\hline
\end{tabular}
\end{table}

APC, main pulmonary artery; APD, right pulmonary artery; RV, right ventricle; Shunt-OX, shunt calculated from oximetric data; Shunt-CD, shunt calculated from cuvette dye curves; Shunt-PD, shunt calculated from pulse densitometer curves; —, oximetry not performed.
The relationship between Shunt-PD and the shunts as calculated from the oximetric data (Shunt-OX) is shown in Figure 4A; Figure 4B shows a Bland-Altman plot of the individual differences. Mean ± SD of the difference between Shunt-PD and Shunt-OX was 0.8 ± 9.8% of Qp, 95% confidence interval –5.4 to 7.0 (n = 12). Mean ± SD of all Shunt-PD and Shunt-OX was 41.5 ± 20.3% of Qp and 40.7 ± 19.7% of Qp, respectively.

Discussion

The data of our study show that the pulse dye densitometry technique allows for accurate quantification of cardiac shunts in patients with congenital heart defects. Despite a slight overestimation in comparison with cuvette densitometry, the pulse densitometer results are in good agreement with the results of the two conventional methods. As there is no gold standard for the
determination of shunts in patients, this demonstrates that a less-invasive measurement by means of the pulse densitometer is at least as good as these two conventional procedures. This implies that most of the practical drawbacks of the conventional dye dilution technique are overcome by this new technique.

The calculation of a left-to-right shunt from an arterial dye dilution curve requires a reliable separation of the normal part and the shunt part of the dilution curve. Therefore, a faithful recording of the dye concentration vs. time curve should be obtained. A pulse densitometer seems a priori more suitable for this purpose than a cuvette densitometer, because the cuvette-sampling system causes a distortion of the recorded dilution curve. The distortion can be diminished by increasing the sampling rate. With the cuvette densitometer of Sutterer and Wood, the usual blood sampling rate was too low for obtaining dye dilution curves, allowing proper separation of the two areas. Therefore, Carter et al. resorted to a method based on the degree of distortion of the descending limb of the dilution curve. For large left-to-right shunts, a reasonable estimation of the shunt thus can be made.

The dynamic response of the pulse densitometer depends on the blood flow rate, the pulsations in the tissue, and the heart rate. Each pulse yields a dye concentration measurement. Figure 2 shows simultaneously recorded dye dilution curves of the cuvette densitometer and the pulse densitometer, following injection of indocyanine green into the pulmonary artery of a patient with a ventricular septal defect. The pulse densitometer curve shows a clear separation of the peak caused by the passage of dye through the defect. In the cuvette densitometer curve, the picture is blurred, although not to the extent that separation of the areas has become impossible. In patient 6, this did happen to be the case and the Carter et al. formula had to be used for the shunt calculation from the dilution curve of the cuvette densitometer. Nonetheless, the agreement between the two densitometers was rather good.

Shunt calculation from oxygen saturation data obtained using multiple samples, taken sufficiently distant from the site of the shunt, may be closest to an acceptable reference method. Such a method has actually been used to validate the present method of shunt calculation. In 33 patients with left-to-right shunts (5–72%), the dye method was compared with the oximetric method, which yielded a mean difference (±SD) of 0.9% (±6.3%). However, the error-free performance of this procedure is difficult and needs several samples. The oximetric data of the present patient study certainly did not qualify for reference status.

However, there are more arguments in favor of pulse dye densitometry as a means for the determination of shunts. First, there is the superior resolution of the normal and the shunt part of the dilution curve (Figure 2). This makes extrapolation of the descending limbs easier and more accurate. Second, the measurement of the dye concentration in small tissue arteries at a short distance from the heart avoids errors through flow effects that easily occur in methods using intravascular detectors, such as platinum electrodes or fiber optic catheters, which have a similar high-dynamic response. When dissolved in distilled water and injected into the blood, indocyanine green binds rapidly enough to plasma protein for the absorption spectrum to stabilize before the blood reaches the site of the densitometer. It remains in the blood long enough for a true concentration-time curve, with recirculation, to be recorded, and it is excreted by the liver rapidly enough to record a washout curve from which the blood volume can be calculated.

Because the shunt can be determined from a single dye dilution curve, the dye dilution method is preeminently suited for the study of the effect of acute changes in cardiovascular conditions, allowing direct assessment of acute (drug-) interventions during a catheterization procedure or during intensive care stay. Using oximetry this can be difficult, because of the need to take at least three blood samples at different sites. Especially during exercise, the accurate determination of mixed venous oxygen saturation is virtually impossible.

This technique may enable a simpler and less invasive procedure to be developed, while gains in precision and accuracy are possible. To that end, the shunt calculation should be automated. Methods to automatically calculate cardiac output and shunts from dye dilution curves have been published previously.

We conclude that pulse densitometry with indocyanine green is suitable for the determination and quantification of left-to-right shunts in patients with congenital heart disease. Thus, an easy and practical method could be attained for the simultaneous and accurate determination of cardiac output, the presence and magnitude of a cardiac shunt, and the total circulating blood volume, after a single injection of indocyanine green, which can be incorporated in the routine
cardiac catheterization laboratory or in the intensive care unit.

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**References**