Pulse Dye Densitometry: A Novel Bedside Monitor of Circulating Blood Volume

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Abstract

<u>Introduction</u>: Monitoring of circulating blood volume is important in the management of critically ill patients. Current methods of circulating blood volume measurements such as indicator dilution using radioisotopes or Evans blue dye are unsuitable for clinical application as these tests do not allow for frequent repeated measurements to be done. A direct bedside measurement of circulating blood volume using the principle of pulse dye densitometry was recently introduced. This is essentially an indicator dilution technique using indocyanine green combined with the principle of pulse spectrophotometry. <u>Methods</u>: This paper aims to review this method of circulating blood volume measurement and provide a summary of the published clinical trials that compared its accuracy with the other conventional methods of circulating blood volume measurement, based on a Medline search, spanning the period 1966 to August 2000. <u>Results</u>: Published studies show that pulse dye densitometry gives comparable results when compared to other conventional methods of blood volume measurement. Its ability to measure circulating blood volume accurately and repeatedly, as frequently as every 20 min makes it suitable for clinical application. <u>Conclusion</u>: Pulse dye densitometry provides for a rapid, semi-noninvasive and convenient bedside assessment of circulating blood volume that is applicable clinically. Further studies are needed to ascertain the impact of the use of pulse dye densitometry on the mortality and morbidity of the critically ill.

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Key words: Circulating blood volume measurement, Indocyanine green, Pulse dye densitometry, Pulse spectrophotometry

Introduction

The monitoring of circulating blood volume (CBV) is important in the care and management of critically ill patients. Progressive blood volume depletion, if unmonitored and uncorrected, can result in tissue ischaemia, acidosis and systemic inflammatory response syndrome.[1,2] Timely recognition and decisive intervention of impending shock is the cornerstone in decreasing the mortality and morbidity in the critically ill. The current available techniques of CBV measurement using the indicator dilution method with radioactive tracers, e.g. radio-iodinated albumin or Evans blue dye, are not clinically applicable. This is because these tracers remain in the blood circulation for days, making frequent and repeated assessment of CBV impossible.

Thus, physicians have relied on indirect clinical parameters such as blood pressure, heart rate, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output, urine output, haemoglobin concentration and haematocrit, to estimate CBV and organ perfusion. Shippy et al,[3] in a review of 1500 critically ill patients, found poor correlation between clinical haemodynamic parameters, such as mean arterial pressure, CVP, PCWP, haematocrit, cardiac output and the extent of blood volume changes. This is because CVP and PCWP, as indirect estimations of right and left ventricular preload, are not only dependent on blood volume, but also on other factors such as intrathoracic pressure, cardiac contractility, posture of the patient and compliance of the capacitance vessels. Shoemaker et al[4] found that the use of these parameters to assess CBV would result in actual volume deficit of between 0.5 L to 2 L in 50% of critically ill patients.

In a previously healthy patient with ongoing haemorrhage, preload to the heart may be maintained in the earlier stages by reflex sympathetic compensatory mechanisms. The use of these indirect clinical parameters may not accurately reflect the true haemodynamic status of the patient and therefore, a delay in adequate fluid resuscitation or surgical intervention may ensue.

Hence, accurate CBV monitoring has a definite role in assisting the physician identify these problems and manage

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fluid resuscitation effectively as well as decide on early surgical intervention. Pulse dye densitometry (PDD) offers the clinician a rapid, semi-invasive and convenient bedside monitor of blood volume. This paper aims to review this method of CBV measurement and provide a summary of the clinical trials that have been conducted to compare its accuracy with other conventional techniques. We conducted a Medline search, spanning the period 1966 to August 2000, using the keywords "pulse dye densitometry", "pulse spectrophotometry and blood volume" and "indocyanine green (ICG)". A total of 15 related articles were found and analysed.[5–19]

Methods of Blood Volume Measurement

The measurement of blood volume has been attempted using several innovative methods. These methods include blood mass densitometry,[20] inhalation of carbon monoxide,[21] combined gas chromatography-mass spectrometry[22] and measurement of cuff-occluded increase in peripheral venous pressure.[23] The main drawbacks of these techniques are that they are mainly laboratory-based and time-consuming.

The dye dilution principle of blood volume measurement involves the administration of labelled markers and tracing their uptake into the body. This principle forms the basis of the use of the pulse dye densitometry.

The Dilution Principle of Blood Volume Measurement

The dilution principle involves the injection of a known quantity of tracer (either a dye or radionuclide) into a fluid compartment, and after thorough mixing, the concentration of the dye in that fluid compartment is measured. The volume of the compartment is determined by dividing the known quantity of dye injected by the concentration of the diluted sample.

$$\text{Volume of compartment} = \frac{\text{Dose of injected dye}}{\text{Drug concentration in compartment after distribution}}$$

Measurement of plasma volume requires the assay of a tracer whose distribution is confined to the plasma space. Likewise, determination of red cell volume requires a marker that tags on specifically to red blood cells. Based on the patient's haematocrit (Hct %), circulating blood volume can either be calculated from red cell volume measured using Cr^{51} labelled red blood cells or from plasma volume using radioiodine-labelled albumin. Other tracers that have been used in the measurement of red cell volume include ^{99m}Tc, ^{111}In, and ^{113m}In.[24] Other plasma markers that have been used include Evans blue dye, ICG and hydroxyethyl starch[25] or fluorescent-labelled hydroxyethyl starch.[26]

Blood volume can then be derived from plasma volume using the following formula (where 0.9 Hct is the average haematocrit of the whole body):

$$\text{Blood volume} = \frac{\text{Plasma volume}}{1 - 0.9 \text{ Hct}}$$

A major drawback with the use of these tracers is their relative long half-life in the bloodstream (Cr^{51} 27.8 days, I^{125} 60 days, I^{131} 8.1 days). Measurements therefore cannot be repeated at regular intervals as a result of dye accumulation. Hence, these investigations are mainly used for research purposes. Other disadvantages of using radioactive tracers include the risks of exposing patients and health care personnel to radiation, the need for special storage and disposal facilities, the need for specially trained personnel and specialised equipment and potential leakage into the perivascular tissues.

Potential sources of errors using the dilution principle include inadequate or delayed mixing (such as low cardiac output states), diffusion barriers or leakage of tracer into another fluid compartment. Importantly, the use of these tracers in septic patients with increased capillary permeability may result in leakage from the intravascular space into the interstitial space, resulting in overestimation of CBV.

Properties of ICG Dye

Since the first use of ICG dye by Fox and Brooker in 1956,[27] this water-soluble tricarbocyanide dye with a peak spectral absorption at 810 nm has been used successfully in the assessment of cardiac output and liver blood flow in both adults and children. ICG binds avidly to serum albumin, which confines its distribution, after an intravenous dose, to plasma. The volume of distribution of ICG has been shown to be comparable to that of radioiodine-labelled albumin[28] or Evans blue dye.[29] Comparative measurements of blood volume in the same patients using ICG and the radioisotope method with Cr^{51}-labelled red blood cells shows an extremely small difference of 1.7% (r = 0.97).[7] The mean difference between two successive plasma volume measurements in the same patient using ICG was 38 mL in this study.

ICG is metabolised solely by the liver (plasma half-life of approximately 4 min) and its plasma concentration declines exponentially after a single intravenous administration. In patients with normal liver function, there is little dye accumulation, allowing repeated measurement of blood volume approximately every 20 min. R15, the index of the percentage of residual ICG in blood 15 min after initial injection, is used to estimate how frequently ICG measurement could be repeated. In a normal individual, the R15 is less than 5%, indicating that 95% of the injected ICG can be cleared by the liver within 15 min.

In patients with severe hepatic dysfunction or portal hypertension, a period longer than 20 min should be allowed for repeated measurements.[30] Patients diagnosed to have hepatic failure with a R15 value of more than 35% can take up to 1 hour to clear 98% of plasma ICG.

ICG can cause an artefactual decrease in haemoglobin oxygen saturation (SpO_2) for up to 10 min and this effect is dose dependent.[31] ICG is well tolerated, although rare cases of anaphylaxis have been reported.[32]

Measurement using the Dye Densitogram Analyser

The principle of pulse spectrophotometry, as developed by Aoyagi et al,[33] is incorporated commercially into the Dye Densitogram Analyser (DDG-2001A/K, Nihon Kohden Tokyo, Japan). The analyser comprises essentially of an optical probe connected to a monitor, and a computer for determination of blood volume and cardiac output.
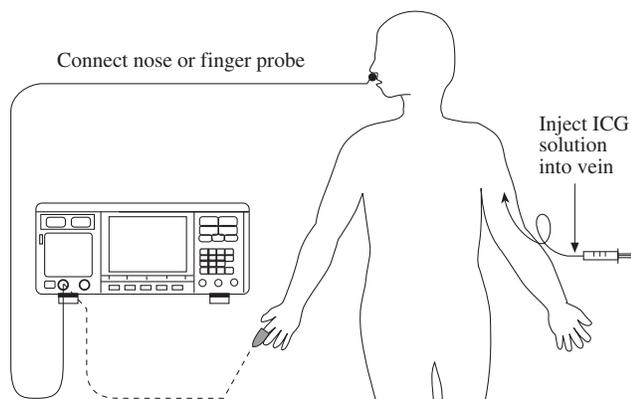

Fig. 1. Set-up of dye densitogram analyser (Published with permission from: Nihon Kohden Singapore from DDG-2001 Analyser Supplemental Information).

The optical probe is similar in construction to that of the pulse oximeter and consists of 2 light emitting diodes (at 805 nm and 890 nm). Both finger and nostril probes are available for attachment to the patient. Pre-injection blood samples are obtained from a peripheral vein and the patient's haemoglobin is measured separately. As ICG can cause a transient decrease in SpO_2, a baseline recording of the saturation is obtained. ICG (in aliquots of 10 to 20 mg) is injected into a peripheral or central vein and blood ICG concentration is measured continuously via the pulse spectrophotometry probe. The haemoglobin concentration is entered into the computer at the end of the determination. Following computation, the early linear dye densitogram, the semi-log dye densitogram and its linear regression line, calculated values of mean transit time (MTT), blood volume and cardiac output are displayed.

Measurement of Plasma ICG Concentration

In *in vitro* spectrophotometry, intermittent optical measurement of the arterial dye concentration is determined by repeated sampling of arterial blood from the patient at 15-min intervals. The main drawback of this method is that the MTT cannot be derived accurately (the plasma concentration of ICG at MTT is needed for computation of blood volume). Moreover, this technique requires arterial cannulation, which entails added risks.

In PDD, the patient's haemoglobin is used as the reference light absorber and the ratio of haemoglobin to arterial ICG concentration is determined non-invasively based on the Beer Lambert's law. Light of 2 different wavelengths, 805 nm and 890 nm, are emitted by the light emitting diode and transmitted through the vascular bed. These wavelengths are selected as the extinction coefficients of oxygenated and deoxygenated haemoglobin at these values are similar. The maximum optical absorption by ICG occurs at 805 nm while absorption is negligible at 890 nm.
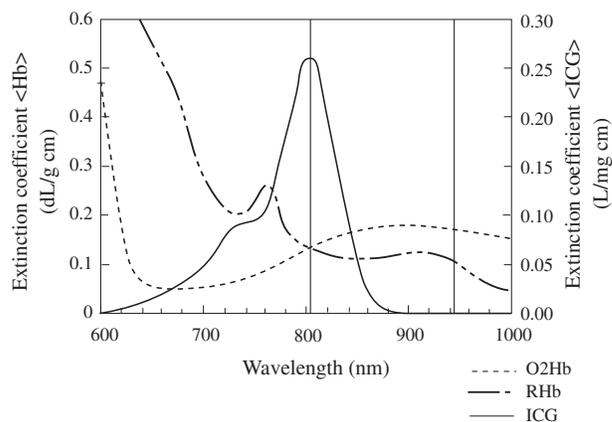

Fig. 2. Extinction coefficient of indocyanine green and haemoglobin (Published with permission from: Nihon Kohden Singapore from DDG-2001 Analyser Supplemental Information).

Pulsatile arterial flow through the vascular beds alters the optical density as well as the path length of light and this change is detected by a photo detector. The ratio of variation induced by the arterial pulsations (AC) to that of the total transmitted light (DC) at 805 nm and 890 nm is dependent on the ratio of arterial ICG concentration and arterial haemoglobin concentration. Using the ratio of AC:DC (805) to AC:DC (890) and measured haemoglobin concentration, the plasma ICG concentration (in mg/L) is computed. A dye-densitogram (DDG) is then plotted, which is essentially the plasma ICG concentration-time curve.
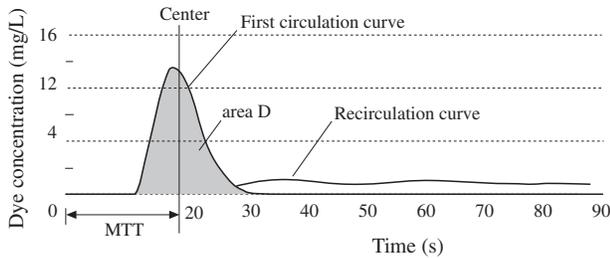
Fig. 3. Dye densitogram recorded using the dye densitogram analyser (Published with permission from: Nihon Kohden Singapore from DDG-2001 Analyser Supplemental Information).

The Dye Densitogram and Determination of MTT

Figure 3 depicts a typical DDG recorded using the dye densitogram analyser after a single intravenous administration of ICG. In view of the temporal delay that will occur as the dye passes via the heart and lungs to the systemic circulation, CBV should be derived from the ICG concentration measured at MTT (C_0), not at initial injection time (MTT is at the centre of gravity of the first circulation and is considered to be the "time zero"). For example, when blood volume was estimated based on the ICG blood concentration taken at initial injection time (before steady state concentration is achieved), the values were underestimated by 8.95% ± 2.33% in adults and 7.30% ± 3.79% in children, as compared to those based on ICG blood concentration at MTT.[13] MTT can be determined using the modified Steward-Hamilton technique, and calculated using the formula[34] (where C_n = ICG concentration at the nth time interval, Dt_n = time interval, t_n = time from the injection at which ICG concentration C_n is recorded).

Figure 4 illustrates a typical semi logarithmic plot of the dye densitogram. C_0 (ICG concentration at injection time after complete mixing but assumed to be before hepatic

$$\text{Mean transit time} = \frac{\Sigma \ (C_n \ x \ Dt_n \ x \ t_n)}{\Sigma \ (C_n \ x \ Dt_n)}$$
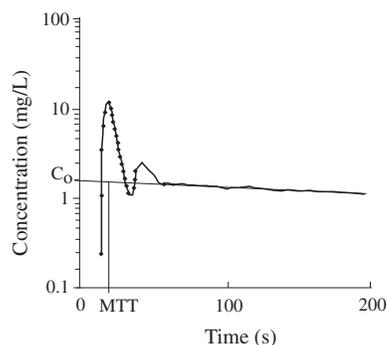

Fig. 4. Semi log plot of the dye densitogram for determination of C_0 (Published with permission from: Nihon Kohden Singapore from DDG-2001 Analyser Supplemental Information).

clearance) is obtained by back extrapolation to the MTT. Iijima et al[35] found that the interval between 2.5 to 5.5 min after MTT is the most ideal period for extrapolation. Blood volume is thus computed from this following equation:

$$\text{Blood volume (mL)} = \frac{\text{Dose of injected ICG dye (mg)}}{\text{ICG concentration } C_0 \text{ (mg/mL)}}$$

Accuracy of Pulse Dye Densitometry as Compared to Conventional Methods

Several clinical studies have been conducted to compare simultaneous measurements of CBV using PPD and the conventional methods.[12,14,35] In each of these "method comparison" studies, the correlation coefficient, bias and precision of each method were compared and analysed.

Barker[36] in his editorial stressed that it would be inappropriate to use the correlation coefficient as a measure of agreement for 2 different methods measuring the same variable. The bias and precision method, as described by Altman and Bland,[37] should be the preferred method for comparison. In essence, bias refers to the mean error, or average of the difference that is obtained by the 2 methods compared during simultaneous measurements. It is a measure of the systematic error or the tendency of one method to read consistently higher or lower than the other. In contrast, precision is the standard deviation of these differences and it is a measure of random error or lack of reproducibility of measurements.

Pulse Dye Densitometry versus *In vitro* Spectrophotometry

Correlation of Blood ICG Concentration Measurement

Iijima et al[35] obtained a percentage bias of 10% (absolute bias of 0.04 mg/L) and a standard deviation of 31% (0.11mg/L) comparing PDD and *in vitro* spectrophotometric measurement. This seemingly large bias is a result of the inclusion of all ICG concentrations (including the 10-min value) for analysis. According to the authors, the low ICG blood concentration at the 10-min reading produced a large error. Exclusion of the 10-min value reduced the imprecision to 3.5% ± 10.5%. In another comparative trial, Imai et al[12] found a bias of -3.9% ± 16.8%. Hence, measurement of blood ICG concentration using PDD was found to agree ±4% with values measured by *in vitro* spectrophotometry (Table I).

Pulse Dye Densitometry and *In vitro* Spectrophotometry

Correlation of Blood Volume Measurement

Based on these different methods of plasma ICG concentration measurements, accuracy in the derivation of

TABLE I: COMPARISON BETWEEN PDD AND *IN VITRO* SPECTROPHOTOMETRY. CORRELATION OF BLOOD ICG CONCENTRATION MEASUREMENT.

Author/year	No. of patients	Nose probe		Finger probe	
		Bias	Precision	Bias	Precision
Iijima et al 1998	10 patients (Healthy volunteers)	10.0% *3.5%	31.0% *10.5%	3.5%	10.5%
Imai et al 1998	25 patients (Major abdominal surgery)	-3.9%	16.8%	3.4%	12.6%

* excluding the 10-min value which correspond to an extremely low ICG plasma concentration
ICG: indocyanine green; PDD: pulse dye densitometry

TABLE II: COMPARISON BETWEEN PDD AND *IN VITRO* SPECTROPHOTOMETRY. CORRELATION OF BLOOD VOLUME MEASUREMENT.

Author/year	No. of patients	Nose probe		Finger probe	
		Bias	Precision	Bias	Precision
Haruna et al 1998	27 patients (Cardiac surgery)	-5.3%	8.7%	-4.2%	9.4%
Iijima et al 1998	10 patients (Healthy volunteers)	2.72%	9.44%	-0.342%	13.97%

PDD: pulse dye densitometry

TABLE III: COMPARISON BETWEEN PDD AND ^{131}I-LABELLED HUMAN SERUM ALBUMIN. CORRELATION OF BLOOD VOLUME MEASUREMENT.

Author/year	No. of patients	Nose probe		Finger probe	
		Bias	Precision	Bias	Precision
Haruna et al 1998	7 patients (Healthy volunteers)	4.2%	4.9%	7.3%	6.9%
Iijima et al 1998	10 patients (Healthy volunteers)	3.9%	10.5%	2.0%	17.9%

PDD: pulse dye densitometry

blood volume was studied. In their clinical trials, Haruna et al[14] and Iijima et al[35] showed that blood volume measurement, derived from plasma ICG concentration using the pulse dye densitometry and *in vitro* spectrophotometry, agreed to within 10% limits (Table II).

Pulse Dye Densitometry and ^{131}I-labelled Human Serum Albumin

Correlation of Blood Volume Measurement

Methods comparison studies have also been carried out to compare the accuracy of blood volume measurement using pulse dye densitometry versus radiolabelled albumin, the current accepted "gold standard" of CBV measurement. In their studies with human volunteers, Haruna et al[14] and Iijima et al[35] demonstrated that PDD estimated blood volume measurements within limits of 4% to 7% when compared to ^{131}I-labelled human serum albumin (Table III).

TABLE IV: LIMITATIONS OF PULSE DYE DENSITOMETRY

Errors related to signal detection by pulse spectrophotometry probe
    Motion artefact
    Poor peripheral circulation
    Presence of abnormal haemoglobin

Errors related to distribution and determination of plasma ICG concentration
    Inadequate mixing, especially in low cardiac output states
    Errors in back-extrapolation from MTT
    Delayed clearance of ICG in patients with significant liver dysfunction
    Over-estimation of CBV in patients with generalised protein capillary leakage

Errors related to derivation of CBV
    Differences in haematocrit from different sampling sites; correction factor not used

CBV: circulating blood volume; ICG: indocyanine green; MTT: mean transit time

Potential Errors and Problems

Table IV summaries the potential sources of error and problems with the use of PDD.

Factors that limit the accuracy of pulse oximetry, for example patient motion and poor peripheral circulation (due to hypotension and vasoconstriction), can result in similar errors in pulse spectrophotometry. Patient motion during the period of measurement has resulted in artefacts in the recorded AC:DC ratio. Heavier probes have been shown to produce more motion artefacts than lighter probes.[38] Haruna et al[14] in their study of 30 patients reported 6 cases of failures attributable to motion artefacts. Dislodgment of the measuring probe by body motion was found to alter the initial measurement conditions and subsequent blood ICG to haemoglobin ratio, rendering the determination of initial dye concentration (C_0) inaccurate.

In low perfusion states, as a result of small pulse amplitude, the fidelity of the AC:DC ratios can be compromised by "noise" artefact, rendering measurement ineffective. In these circumstances, the AC:DC ratio from a nose probe is found to be accentuated when compared to that from the finger probe (secondary to greater perfusion of the face). Iijima et al[35] found that the frequency of variations of CBV as measured by a finger probe was twice that for a nasal probe.

Measurement errors due to variations in haematocrit value can be expected if the blood is taken from different sampling sites. Large vein haematocrit (LVH) has a higher value compared to whole body haematocrit (WBH), which can lead to an overestimation of blood volume. The F cell ratio, which is defined as the ratio of LVH to WBH, is found to be in the range of 0.90 to 0.95 in trauma patients, and 0.89 to 0.94 in anaesthetised patients; hence, a constant correction factor of 0.91 has to be applied.[39,40]

The accuracy of PDD in patients with generalised inflammation (sepsis, burns) has not yet been evaluated. In these patients with impaired capillary integrity, leakage of ICG from the circulation into the interstitial space could theoretically lead to an overestimation of blood volume. Simultaneous measurement of the initial distribution volume of glucose (IDVG) and ICG has been studied[41,42] and the plasma volume ICG to IDVG ratio can be used as an index of overestimation of CBV due to capillary leakage. A normal ratio indicating the absence of leakage ranges between 0.25 to 0.45, while a ratio >0.45 suggests leakage and overestimation in derived results.[43] This study recommends simultaneous measurement of IDVG and ICG in critically ill patients.

Clinical Applications

All the published studies so far have suggested that PDD is comparable to conventional methods of measuring CBV and this technique can be applied in the clinical setting. But will it change our practice paradigms and decrease morbidity and mortality rates in our patients? We opine that PDD may have a role in certain clinical situations. For example, a previously healthy patient who has sustained a blunt abdominal injury is admitted to the intensive care unit for observation. He may have occult intraabdominal bleeding that may require eventual surgical intervention, but which may not be clinically apparent initially due to sympathetic compensatory mechanisms. With the use of PDD, we can measure CBV repeatedly and monitor the occult blood loss. Based on this additional haemodynamic parameter, early decisive surgical decision can be reached. This may result in decreased morbidity and mortality as well as reduce the use of blood and other blood products. For the less experienced clinician, the extra information on CBV status may improve the management of the critically ill patients.

To date, there are no published studies on the impact of PDD on the mortality and morbidity of the critically ill. Useful data in this regard may not be forthcoming, as PDD is merely a monitoring modality, not a therapy. The information it offers is only as good as the clinician who interprets it.

Conclusion

PDD provides for a rapid, precise and convenient bedside assessment of CBV that promises to be clinically applicable in the near future. However, before PDD can be recommended as one of the "standard critical care monitors" in the intensive care units and operating theatres, further clinical studies should be conducted to determine its clinical utility and cost-effectiveness.

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