

Measuring circulating blood volume in newborn infants using pulse dye densitometry and indocyanine green

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Summary

Background: Circulating blood volume (BV) is an important, but often unconsidered, variable in newborn infants undergoing intensive care. The data on validation and repeatability of BV measurement are limited.

Aim: To validate and test the repeatability of measuring BV in newborn infants using indocyanine green (ICG) and pulse dye densitometry (PDD).

Methods: Validation – Paired measurements of BV were made using the fetal hemoglobin (HbF) dilution and the PDD method.

Repeatability – The BV was measured twice at an interval of 30–40 min in a second group of infants.

Results: Validation – Data from three of 13 infants studied were excluded because of probe dislodgement or ICG injection error. The median (range) birth weight of the 10 infants whose data were analyzed was 1032 g (740–2384 g) and seven (70%) were receiving either mechanical ventilation or nasal CPAP. The median BV measured by HbF dilution was $66.2 \text{ ml}\cdot\text{kg}^{-1}$ ($43.7\text{--}81.0 \text{ ml}\cdot\text{kg}^{-1}$) and by the PDD method was $68.9 \text{ ml}\cdot\text{kg}^{-1}$ ($49.3\text{--}101.0 \text{ ml}\cdot\text{kg}^{-1}$). The mean difference was $5.92 \text{ ml}\cdot\text{kg}^{-1}$ ($\text{SD } 17.33 \text{ ml}\cdot\text{kg}^{-1}$). **Repeatability** – Twelve infants were studied and three excluded because of probe dislodgement/motion artifact or ICG injection error. The median weight of the nine infants whose data were analyzed was 1208 g (795–2600 g). The median (range) BV1 and BV2 were $70.5 \text{ ml}\cdot\text{kg}^{-1}$ ($53.1\text{--}160 \text{ ml}\cdot\text{kg}^{-1}$) and $87.5 \text{ ml}\cdot\text{kg}^{-1}$ ($38.0\text{--}248.0 \text{ ml}\cdot\text{kg}^{-1}$), respectively. Mean difference of the two BV estimates (BV1–BV2) was $-24.6 \text{ ml}\cdot\text{kg}^{-1}$ ($\text{SD } 33.3 \text{ ml}\cdot\text{kg}^{-1}$) and coefficient of repeatability was $66.5 \text{ ml}\cdot\text{kg}^{-1}$.

Conclusion: Pulse dye densitometry can be used to measure BV in the newborn infant at the cotside but the repeatability measurements suggest that its use is limited.

Keywords: blood volume; pulse dye densitometry; indocyanine green; newborn infant; circulation

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Introduction

Appropriate management of hemodynamic changes is important to prevent morbidity and mortality of sick newborn infants (1). Circulating blood volume (BV) is an important, but often unconsidered, variable in the newborn infants undergoing intensive care. Many clinical studies describe the administration of boluses of fluid to expand the total circulating BV in response to clinical signs of poor skin perfusion, hypotension or acidosis and yet studies both in adults and in the newborn infants (2) show the prediction of hypovolemia by clinical assessment to be poor.

At present, a simple cotside method to measure BV of newborn infant is not available. The monitoring of BV, if sufficiently practical and accurate, may be a useful addition to intensive care monitoring repertoire and could affect patient treatment and therefore outcome. Methods used previously involving the injection of autologous red blood cells labeled with biotin (3), fetal hemoglobin (HbF) dilution (4) or repeated blood sampling following injection of a marker such as indocyanine green (ICG) (5) are not suitable for routine clinical practice; radio-labeled methods are not acceptable for newborn infants. The data on testing for validation and repeatability of BV measuring methods in newborn infants are limited.

Aoyagi (6) developed a bedside method of measuring BV using pulse dye densitometry (PDD) and ICG. PDD also measures cardiac output (CO) and liver blood flow or function. Good agreements have been reported between CO measured by PDD and that measured by thermodilution method in adults using a Swan-Ganz catheter (7). However, Bremer *et al.* (8) found that the agreement was poor in critically ill patients with low CO. The BV measured by PDD in adult volunteers and sick patients agrees well with the BV measured by ^{131}I -labeled human serum albumin (^{131}I -HAS) method (9,10) as well as ^{51}Cr -labelled red blood cells (11). The PDD-ICG method has been successfully used in a multicenter study of BV measurement in adult surgical patients during general anesthesia in Japan (12).

The objective of this study was to validate and test the repeatability of the measurement of BV in newborn infants at the cotside using PDD and ICG. The validation was performed by simulta-

neously measured BV using the HbF dilution method as described by Phillips *et al.* (4).

Method

Validation of PDD method

Paired measurements of BV were performed at the time of the first blood transfusion by the PDD method (BV_{PDD}) and the HbF dilution technique (BV_{FHD}) as reported by Phillips *et al.* (4).

Repeatability of PDD method

The BV was measured twice at an interval of 30–40 min in infants whose cardiorespiratory function was stable and who had an intravenous (i.v.) cannula for clinical indication.

Blood volume measurement procedure

Pulse dye densitometry and ICG method

The PDD analyzer used in this study was the DDG-2001 (Nihon Kohden Corp., Tokyo, Japan). The PDD probe was placed on the finger or toe of the infant and calibrated. A bolus of ICG ($0.2 \text{ mg}\cdot\text{kg}^{-1} = 0.2 \text{ ml}\cdot\text{kg}^{-1}$; ICG-Pulsion, Pulsion Medical System AG, Munich, Germany) was injected rapidly through an existing umbilical or peripheral venous cannula. The continuous arterial blood ICG concentration was measured noninvasively for 10–15 min. The infant's hemoglobin determined pre-ICG injection was entered into the PDD analyzer.

Indocyanine green injection procedure

Accurate dose of ICG ($0.2 \text{ mg}\cdot\text{kg}^{-1} = 0.2 \text{ ml}\cdot\text{kg}^{-1}$) measured using 1-ml syringe (BD Plastipak; Backton Dickinson SA, Madrid, Spain). The syringe with ICG was connected to an extension set with 'T' adapter (Venisystems, Hospira, Ireland) through a three-way stopcock (Pharmaceutical Laboratory, VYGONF, ECOUEN, France) to prevent disconnection during rapid bolus injection. This set was connected to an existing baby's peripheral (BD Neoflon, Beckton Dickinson Infusion Therapy AB, Sweden) or central (Kids CathTM Umbilical, Ruger Medical, Germany) i.v. cannula.

The extension tube of the injection circuit was filled with ICG. The start key on the front panel of

DDG-2001 was pressed and a bolus of 1.5–2 ml of normal saline (B|BRAUN Medical Ltd, Sheffield, UK) was injected rapidly so that the ICG solution was injected as quickly as possible.

The BV (ml) was calculated by the equation

$BV = I/CD_0$ where I is the injected ICG dose (mg) and CD_0 is the concentration of dye ($mg \cdot 100 \text{ ml}^{-1}$) in blood computed by back-extrapolation of the clearance curve to the mean transit time (MTT) point of the first dye circulation. This time point is assumed to be the beginning of elimination of dye by the liver (7).

Principle of pulse dye densitometry

Pulse dye densitometry is based on the principle of pulse spectro-photometry (7), which is based on the Beer–Lambert law. It relates the concentration of a solute to the intensity of light transmitted through a solution. PDD uses wavelengths of 805 and 890 nm to measure the ratio of ICG concentration to hemoglobin concentration. The peak optical absorption of ICG occurs at 805 nm and almost zero optical absorption occurs at 890 nm. The optical probe is essentially the same as that used for pulse oximetry but using different wavelengths. Accordingly, the ICG concentration can be calculated from the ratio of its concentration to the hemoglobin concentration for each pulse, using the known hemoglobin value ($mg \cdot dl^{-1}$) (7,13).

Fetal hemoglobin dilution method

Knowing the volume of red blood cells being transfused, the pretransfusion BV (BV_{FHB}) can be calculated as follows (4):

$$BV_{FHD} = \frac{V \times HbF_{post}\%}{Hct_{pre}(HbF_{pre}\% - HbF_{post}\%)} (\text{ml of blood}),$$

where V is the volume of red blood cells transfused in ml, $HbF_{pre}\%$ is the percentage of HbF before transfusion, $HbF_{post}\%$ is the percentage of HbF after transfusion and Hct_{pre} is the pretransfusion hematocrit. HbF was measured by HPLC (Varient; Bio-Rad, Minnesota, USA) and hematocrit was measured by an automated full blood count analyzer (SE9500; Sysmex, Kobe, Japan).

Table 1

Details of infants' data analyzed

Clinical parameter	PDD validation (n = 10)	PDD repeatability (n = 9)
Birth weight (g)	1032 (740–2384)	1208 (795–2600)
Gestational age (weeks)	28 (24–40)	29 (23–40)
Age at test (days)	3 (1–27)	7 (2–27)
Ventilation/CPAP (n)	7 (70%)	4 (44%)

Values are in expressed as median (range); n, number of infant.

Subjects

The study was approved by the Local Research Ethics Committee and informed written parental consent was obtained.

Validation of PDD method

A total of 13 infants needing their first blood transfusion were studied. Data from three were excluded because of probe dislodgement ($n = 2$) or ICG injection error. Successful paired measurements using the two different methods were made from 10 infants (Table 1). All the infants studied had normal pH and blood pressure. There was no change in the infants' heart rate during entire BV measurement procedure. No complication was noted related to either the equipment or ICG injection.

Repeatability of PDD

A second group of 12 infants was studied and three excluded because of probe dislodgement or motion artifact ($n = 2$) and ICG injection error. Successful paired measurements were made from nine infants (Table 1). All the infants studied had normal pH and blood pressure. There was no change in the infants' heart rate during entire BV measurement procedure. No complication was noted related to either the equipment or ICG injection.

Statistical analysis

The agreement between the two methods and repeatability was analyzed by the method of Bland and Altman and coefficient of repeatability. All the data were expressed as median with range.

Result

The details of the infants studied are shown in Table 1.

Validation of the PDD method of measuring BV

Paired measurement of BV by PDD and the HbF dilution method is shown in Table 2. The correlation between BV measured by PDD and by HbF dilution method was 0.39 (Figure 1). Using the method of Bland and Altman, it is seen that the mean difference between the two methods was 5.92 ml·kg⁻¹ and the standard deviation was 17.3 ml·kg⁻¹ (Figure 2).

Repeatability of PDD method

The two BV measurements by PDD within a 30- to 40-min interval are shown in Table 2. The mean

Table 2
Blood volume result (BV)

Measuring method	PDD-ICG	HbF dilution
Validation of the PDD method		
Median BV (ml)	80.0 (50.0–150.0)	64.1 (35.0–185.3)
Median BV (ml·kg ⁻¹)	68.9 (49.3–101.0)	66.2 (43.7–81.0)
Measuring method	PDD-ICG (measurement 1)	PDD-ICG (measurement 2)
Repeatability of the PDD method		
Median BV (ml)	120.0 (40–200)	120.0 (67.4–310.0)
Median BV (ml·kg ⁻¹)	70.5 (53.1–160)	87.5 (38.0–248)

Values in parenthesis are range.

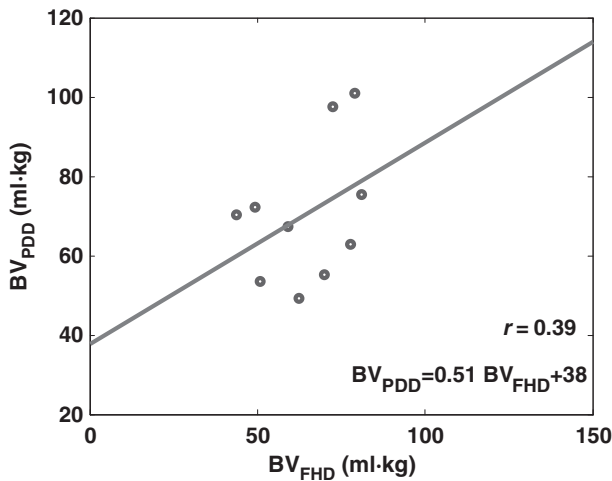


Figure 1
Correlation of blood volume (BV) measured by the pulse dye densitometry and fetal hemoglobin dilution (FHD) methods. Each point represents one measurement in a separate infant.

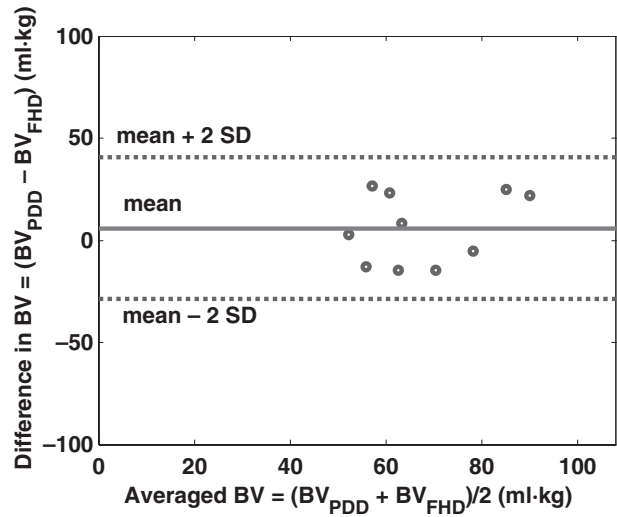


Figure 2
Bias of blood volume (BV) obtained using the fetal hemoglobin and pulse dye densitometry methods.

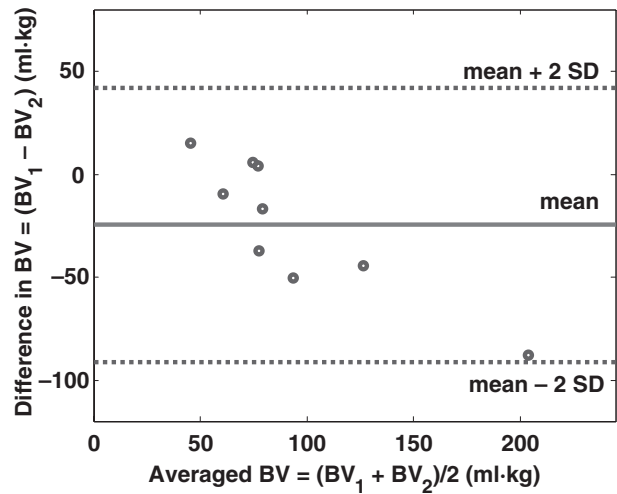


Figure 3
Bland–Altman analysis: repeatability of the pulse dye densitometry method.

difference of the two BV estimates (BV₁–BV₂) was –24.6 ml·kg⁻¹ with a standard deviation of 33.3 ml·kg⁻¹ (Figure 3). The coefficient of repeatability was 66.5 ml·kg⁻¹.

Discussion

We have made simultaneous measurement of BV by PDD with ICG and the HbF dilution method in stable full-term and preterm infants. Measuring BV

in newborn infants at the bedside is feasible using the PDD method. The measured BV result is available within 15–20 min and is noninvasive apart from injecting ICG. The BV measured by the two methods was comparable with bias of $5.92 \text{ ml}\cdot\text{kg}^{-1}$ and SD of $17.3 \text{ ml}\cdot\text{kg}^{-1}$. However, the repeatability of BV measurement by PDD-ICG method was poor with bias of $-24.6 \text{ ml}\cdot\text{kg}^{-1}$ and SD of $33.3 \text{ ml}\cdot\text{kg}^{-1}$.

Indocyanine green

Indocyanine green is a tricarbo-cyanine dye. It is firmly bound to plasma proteins, excreted in bile in unconjugated form, and rapidly eliminated by the liver within 10–15 min (14). ICG has been used for clinical investigations such as measuring hepatic blood flow, testing liver function and measuring CO for more than 40 years. In the last two decades, ICG has been used for measuring circulating BV in adults and newborn infants (5). ICG has been demonstrated to be safe to use in adults and in full-term as well as preterm infants (5,15).

Validation of PDD

The BV measured by the PDD-ICG method agreed with the BV measured by HbF dilution method in the present study. The HbF dilution method has been validated by comparing it with the BV measured by biotin-labeled red cells (3) and ICG dilution method (16) but not tested for repeatability. Testing

for repeatability of the HbF, dilution method is not practical or ethical as this requires adult blood transfusion (4). The present study BV measured by PDD and HbF dilution methods are approximately the same as the reported BV measured by ^{32}P -labeled autologous red cells dilution (17), Evans blue dye dilution (18), ^{125}I -human serum albumin dilution (19), adult Hb dilution and biotin-labeled red cells dilution (2) methods in newborn infants (Table 3). Reports of BV measured by the ICG dilution method in newborn infants are limited (15,20) (Table 3).

Blood volume measured by the albumin-labeled indicator dilution method may overestimate the actual circulating BV as it may measure 'albumin space' due to capillary leak (21). This effect is unlikely to happen to BV measured by PDD as only the first few minutes of the dilution curve are used in the estimation of ICG concentration (MTT + 2.5 min to MTT + 5.5 min). Biotin-labeled red cell dilution is the gold standard method of measuring BV in newborn infants as the radio-labeled indicator dilution methods are not acceptable. The biotin-labeled method has been validated in healthy adults (22). Recently, the repeatability of biotin-labeled red cell dilution method has been confirmed in healthy adult volunteers (23). Hudson *et al.* demonstrated that the BV measured by the HbF dilution is similar ($r = 0.989$) to the biotin-labeled red cell dilution method in newborn infants. Neither the ranked pair differences nor the median of the two estimations

Table 3
Measured blood volume reported in the literature

References	Subjects studied	Measurement method	Blood volume ^a ($\text{ml}\cdot\text{kg}^{-1}$)
Mollison <i>et al.</i> (17)	No. infants: 28 Gestation: full-term	RCV – ^{32}P -labeled autologous RBCs dilution PV – Evans blue dye dilution BV estimated by adding RCV and PV	84.7 (68.5–100.3)
Low <i>et al.</i> (18)	No. infants: 50 Gestation: full-term	Evans blue dye dilution	76.5 (59–100)
Linderkamp <i>et al.</i> (19)	No. infants: 14 Gestation: 26–29 weeks	^{125}I -human serum albumin dilution	76.8 ± 4.9 (range not reported)
Aladangady <i>et al.</i> (2)	No. infants: 38 Gestation: 24–32 weeks	Biotin-labeled RBCs dilution	71.0 (53–105)
Leung <i>et al.</i> (15)	No. infants: 17 Gestation: 23–40 weeks	ICG dilution	70.8 (16.4–140.6)
Nagano <i>et al.</i> (20)	No. infants: 25 Gestation: 24–39 weeks	ICG dilution	94.9 (50.0–158.0)

RCV, red cell volume; PV, plasma volume.

^aValues are in expressed as mean (range).

was significantly different. However, the authors have not tested for bias and precision (3). The BV measured in this study by PDD is comparable and agrees with simultaneously measured BV by the HbF dilution method. None of the infants studied was edematous or suspected of having capillary leak syndrome.

Repeatability of PDD

The repeatability of BV using the PDD-ICG method was poor in the present study. The second BV measurement was higher than the first BV value on three of nine occasions. The second BV was measured 30–40 min after the first measurement. This should allow sufficient time for the first ICG bolus to be completely cleared from the system. Even in the presence of ICG from the first BV measurement, the effect on the second BV measurement will be a higher ICG concentration (CD_0) which would have led to a smaller BV value, not a higher value as we observed. Again no infant studied was edematous; all infants were stable and there was no change in their clinical condition between the first and the second BV measurement. The routinely monitored serum bilirubin ($11\text{--}165\ \mu\text{mol}\cdot\text{l}^{-1}$) was within normal limit for this population. We are not able to explain the reason for the larger value of the second BV measurement (Table 2). It is also noted that the difference between the measurements is greater at higher average BV (Figure 3). This can be explained by the statistical error in analysis that error in BV measurement is proportional to the real BV, i.e. $\delta BV = (\partial BV/\partial I)\ \delta I + (\partial BV/\partial CD_0)\ \delta CD_0 = \delta I/CD_0 - (\delta CD_0/CD_0)\ BV$. This equation describes the change in BV (i.e. δBV) caused by a change in I and/or CD_0 (i.e. δI and δCD_0) and we can see that δBV is proportional to BV itself. In other words, the larger the real underlying BV, the larger the error of the BV measurements.

Data on repeatability of BV measuring methods are very limited even in animals and adults. BV measurements by carbon monoxide (pigs; $n = 6$) (24) and biotin-labeled red cells (adult volunteers; $n = 4$) (23) have been tested for repeatability with variable results. Kisch *et al.* (25) demonstrated the reproducibility of measuring BV by the Evans blue dye dilution in piglets ($n = 11$) using a fiberoptic

catheter placed in the femoral vein. Imai *et al.* (11) demonstrated the good repeatability of PDD-ICG method in adults by measuring BV in eight intensive care patients. As far as we know, this is the first report of testing for both validation and repeatability of BV measurement in newborn infants.

Overall, the data from six infants studied (four probe dislodgement or motion artifact and two ICG injection error) were excluded because of failure to produce a proper ICG clearance curve and to estimate the initial ICG blood concentration. This is comparable to the reported artifact rate in near infrared (NIR)-based studies in adult volunteers (9) and newborn infants (15). Some of this problem may be reduced by improving or developing a probe specifically for newborn infants. We think that these problems were increased because the technique was being learned and that the failure rate would fall with experience. The dose of ICG given to the infants was very small (0.2–0.5 mg or 0.2–0.5 ml). The accuracy of the estimate of BV is dependent upon the accuracy with which this small dose is drawn up and administered. The i.v. site used for injecting ICG was also not uniform; the umbilical venous cannula (UVC) was used when it was available, otherwise an existing peripheral i.v. cannula on the upper or lower limb was used.

In conclusion, the PDD-ICG method can be used to measure BV in the newborn infant at the cotside but the repeatability measurements suggest that its use is limited. Further improvement and studies to determine the limits of its absolute accuracy and repeatability are needed to assess fully its role in the clinical setting.

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Conflict of interest

None.

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