Impact of the time window on plasma volume measurement with indocyanine green

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Abstract

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Abstract
Recent reports have questioned the accuracy of the indocyanine green dilution technique for measuring plasma volume. Our objective was to evaluate the impact of different time windows for monoexponential extrapolation. We retrospectively analysed 31 indocyanine green decay curves to investigate the problem in principle (group 1) and prospectively performed another 21 plasma volume measurements to estimate its practical impact (group 2). To monoexponentially extrapolate back to the specific extinction at the time of dye injection, two different time windows were applied to each decay curve, comparing the plasma volumes resulting from sampling within a short (≤ 5 min) versus a longer (> 5 min) period of time. Extrapolating back from the longer period led to a higher apparent plasma volume relative to the shorter period in both groups, the difference being 348 ± 171 ml (group 1) and 384 ± 131 ml (group 2; mean ± SD; p < 0.05 each). This result was due to a reliable monoexponentiality of decay only up to the 5th min after dye injection. Thus, to estimate the initial distribution space of indocyanine green via monoexponential extrapolation, the first linear kinetic of indocyanine green decay should be taken.

Keywords: plasma volume, indocyanine green, tracer dilution, extrapolation, dye decay, two-compartment model

¹ Both authors contributed to this work in equal parts.
**Introduction**

Plasma volume (PV) is the target of infusion therapy, and its exact measurement is an important clinical and scientific option (Jacob *et al* 2007). Indocyanine green (ICG), besides monitoring hepatosplanchnic blood flow (Sakka *et al* 2007, Stehr *et al* 2005), has been frequently used for PV measurements (Belin de Chantemène *et al* 2006, Bradley and Barr 1968, Haller *et al* 1992, 1993, Jacob *et al* 2003, 2007, Rehm *et al* 1998, 2000a, 2000b, 2001). Although PV is intra-individually inconstant, validation of this method has been performed successfully (Haneda and Horiuchi 1986, Jacob *et al* 2007, Menth-Meier *et al* 2001). Repeatability of the ICG-dilution technique (ICG-DT) has been shown to be excellent (Haller *et al* 1993, Rehm *et al* 1998) as has the accuracy (Menth-Meier *et al* 2001), provided circulatory steady-state conditions are maintained between two corresponding measurements (Jacob *et al* 2007). Generally, after injection of a known amount of dye into a fluid compartment, its concentration after complete mixture allows the calculation of the total volume of this compartment. Despite plasma being the primary distribution space of intravenously injected ICG (Jacob *et al* 2007), a direct approach is not possible for measuring total PV. Due to its short intravascular half-life, a significant portion of the injected ICG is removed from the plasma already during mixing time. Consequently, it is necessary to take as many timed samples as possible after a complete mixture with the plasma, measuring ICG concentrations in each of them, and then to extrapolate back to the concentration at the time of injection. This yields a theoretical value never really existing in plasma, but necessary for the calculation of PV (Jacob *et al* 2007). Non-invasive transcutaneous pulse spectrophotometry (Goy *et al* 2001, Iijima *et al* 1997, 1998, Imai *et al* 1998) is based on the same principle.

Concern exists with respect to the ICG technique, as there is no standard approach for performing the extrapolation. As a result, ICG-DT has occasionally been reported to overestimate PV (Ishihara *et al* 2002, Jones and Wardrop 2000, Mi *et al* 2003). In several investigations performing monoexponential extrapolation (Jacob *et al* 2003, Rehm *et al* 2000a, 2001), we have qualitatively observed the ICG decay to be reliably linear between the 2nd and the 5th min after injection and often, but inconstantly, to flatten after this time window. Therefore, our standard extrapolation has excluded measuring points beyond the 5th min (Jacob *et al* 2007). The goal of our present investigation was (i) to quantify this anecdotic observation in principle (group 1, see below) and (ii) to demonstrate the practical impact of ignoring this fact by means of comparing our extrapolation modality to one exemplarily taken from literature (group 2). Our aim was to provide a reliable and simple extrapolation technique to the general clinical user.

**Materials and methods**

The study was approved by the ethics committee of our institution. All patients and volunteers gave written informed consent and were all risk classification 1 or 2 of the American Society of Anesthesiologists. The patients (group 1) were female, suffered from carcinoma of the cervix and were scheduled for radical hysterectomy. The volunteers (group 2) were healthy males. We performed PV measurements in each patient and volunteer using the ICG dilution method: dye was injected and the theoretical concentration at injection time ($C_{t0}$) was derived from the decay curve by monoexponential extrapolation after complete mixture.

Group 1 is a retrospective analysis of already existing dilution curves in order to generally compare time windows up to minute 5 to one exceeding the 5th min, i.e., to investigate the problem in principle. Thirty-one ICG decay curves had been derived from 31 individual, fully relaxed patients 20 min after induction of general anaesthesia under stable haemodynamic
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(70 < MAP < 90 mmHg, 60 min\(^{-1} < \text{HR} < 100 \text{ min}^{-1}\), continuous application of norepinephrine < 5 \(\mu\text{g kg}^{-1}\text{ h}^{-1}\)) and volume states and before starting the surgical procedure. No bleeding or fluid infusion, except for very small amounts which were necessary to inject the intravenous drugs, occurred before the measurement procedure. We calculated two apparent plasma volumes for each patient, one resulting from monoexponential extrapolation using a short (2nd to 5th min) and the other from using a longer (2nd to 9th min) time window. The length of the time window was the only difference between the two theoretical, retrospective approaches. The PV values resulting from the short time window have been, in part, published previously (Jacob et al 2003, Rehm et al 2000a, 2001).

Group 2 comprises a prospective comparison of two different ICG dilutional techniques to assess PV. The intention behind this part of the study was to transfer a theoretically identified problem into practical impact. We applied two different monoexponential approaches from literature to the dye decay of each volunteer and compared the resulting plasma volumes. Besides the length of the time window, the approaches also differed concerning the starting point of sampling (2nd versus 3rd min) and the time interval between measuring points (20 versus 60 s).

**Theoretical background of PV determination with ICG**

In group 1 we had used the ‘whole blood’ method (Jacob et al 2007). In addition to the scientific character of the measurements, this method provides PV almost ‘online’, which can be useful in the perioperative setting. However, it requires an arterial line for technical and theoretical reasons: to obtain specific extinction, i.e., extinction only caused by ICG in a blood or plasma sample, it is necessary to subtract the basal extinction at 900 nm (no ICG extinction) from the total extinction at 800 nm (maximum ICG extinction). For a whole blood sample, the basal extinction is mainly caused by plasma and red cells. In venous blood, the oxygen saturation of haemoglobin and, thus, basal extinction at 900 nm is not constant. Therefore, fully oxygenated arterial blood is required when using the ‘whole blood’ method. The calculation (see below) includes a subtraction of the total volume of the red cells in the blood sample.

In group 2 we abstained from an arterial line, because no ‘online’ PV was required in these scientific measurements. Thus, we employed the ‘plasma’ method (Jacob et al 2007): the venous samples were centrifuged and the specific extinction was determined in a series of plasma samples. Consequently, a subtraction of the red cell volume in the sample is unnecessary, making the calculation simpler in group 2 (see below).

**Data acquisition in group 1**

General anaesthesia was induced with fentanyl, thiopental and cis-atracurium, and, after tracheal intubation, anaesthesia was maintained with 0.4–1.5 vol% isoflurane in a 50% oxygen–nitrous oxide mixture. Mechanical ventilation was performed to maintain arterial oxygen partial pressure at 200–250 mmHg and arterial carbon dioxide partial pressure at 40 ± 5 mmHg. Radial artery and central venous catheters were inserted. Cooling of the patients was prevented by means of a warming blanket. Perioperative monitoring included electrocardiogram, direct arterial blood pressure, pulse oximetry, repeated determinations of haemoglobin concentration (at least every 30 min; cyanhaemoglobin method) and arterial blood gases. Additional doses of fentanyl and cis-atracurium were given as appropriate.

Immediately before each dye injection, a two-point calibration was performed by measuring two 10 ml aliquots of the patients’ arterial blood containing known ICG
concentrations (1.25 and 2.5 µg ml\(^{-1}\) of whole blood, respectively; ICG, Paesel, Frankfurt, Germany). The light absorption of the blood was measured spectrophotometrically at 800 and 900 nm (Haller et al. 1992). After calibration, 0.25 mg ICG per kg body weight was injected into the central venous catheter as a bolus dose over 5 s at \(t_0\). For measuring ICG concentration, blood was continuously withdrawn from the arterial catheter through a cuvette by means of a calibrated pump (20 ml min\(^{-1}\)), slightly heparinized and immediately reinfused. Consequently, no net loss of blood occurred and the recording of the specific light absorption was without interruption during the 9 min following dye injection (Jacob et al. 2007).

**Data acquisition in group 2**
The healthy subjects rested in a supine position for 40 min. Calibration was performed with two plasma samples, supplemented with known amounts of ICG, resulting in two known concentrations (1.25 and 2.5 µg ml\(^{-1}\) of plasma, respectively). ICG (0.25 mg kg\(^{-1}\)) was then injected into a peripheral vein as a bolus dose over 5 s at \(t_0\) and venous samples (2.5 ml each) were taken every 20 s between the 2nd and the 5th min. Additionally, we took samples at minutes 6 and 7. The blood samples were centrifuged and ICG dilution determined as described elsewhere (Haller et al. 1992).

**Calculation of PV**
The concentration of ICG at \(t_0\) was derived by monoexponential extrapolation of the light-absorption curve, resulting from the respective measuring time points, back to \(t_0\). For group 1, putting this absorption value into the whole blood calibration curve yielded \(CB_0\), the theoretical whole blood concentration of the dye at \(t_0\). The theoretical plasma concentration of the dye at \(t_0\) (\(CP_0\)) was then calculated as \(CP_0 = CB_0/(1 - HKLV)\), where HKLV represents the large vessel haematocrit determined in blood samples withdrawn from the arterial line. PV can then be calculated according to \(PV = D/CP_0\), \(D\) being the amount of dye injected.

In group 2, extrapolation and calibration led directly to \(CP_0\). PV was then calculated as described above.

**Time windows**
In group 1, two different ranges of measuring times within each one of the ICG decay curves were used for extrapolating back to the ‘theoretical’ specific light absorption at \(t_0\) (\(E_{s0}\)). Consequently, we were able to compare two corresponding values of PV for each patient. The values were derived from measuring points taken from the curve every 10 s between the 2nd and the 5th min (PV\(_{2–5}\)) and between the 2nd and the 9th min (PV\(_{2–9}\)) after dye injection, respectively.

In group 2, two practically used monoexponential extrapolation modalities were compared. According to Jacob and Rehm (Jacob et al. 2003, Rehm et al. 1998, 2000a, 2000b, 2001) we derived the PV from samples obtained between the 2nd and the 5th min (PV\(_{early}\)). Due to the requirement of manual sample withdrawal when using the plasma method (Jacob et al. 2007), the interval between measuring points has to be extended versus group 1 to 20 s for technical reasons, resulting in ten measuring points to be used for extrapolation of apparent PV\(_{early}\). Other groups have applied monoexponential extrapolation using time windows up to the 7th (Mi et al. 2003) or even the 11th min (Ishihara et al. 2002). To derive such PV\(_{late}\) values we exemplarily chose the approach of Mi and co-workers, because the authors had questioned the accuracy of ICG-DT in general (Mi et al. 2003). This approach takes five samples in total into consideration, withdrawn every 60 s between the 3rd and the 7th min.
Values right at the beginning of the curve are occasionally not log-linear with respect to the following values, indicating an incomplete mixing. Such values were excluded from extrapolation in all groups starting their measurements at the 2nd min. The criterion was the $R^2$ value of the initial six extinction values: whenever this lay under 0.99, measurements at the beginning were sequentially excluded from extrapolation until the next six consecutive values yielded an $R^2$ higher than 0.99 in the semi-logarithmic plot.

Statistical analysis

All measured ICG concentrations and calculated PV data were distributed normally (assessed by Kolmogorov–Smirnov tests) and are presented as mean ± SD. For assessing intergroup differences, paired Student t-tests were performed. $P < 0.05$ was considered significant.

Results

An exemplary and representative ICG dilution curve from group 2 is displayed in figure 1. The black squares indicate the ten measuring points between the 2nd and the 5th min which lead to PV early via $E_{01}$. The white triangles represent the five measuring points leading to PV late via $E_{02}$. The higher apparent extinction value at $t_0$ found with the early time window corresponds to a smaller calculated volume of distribution, i.e., PV.

A very tight relationship between plasma volumes derived from measuring points before the 5th minute and those based on data beyond that point of time was observed in both groups ($r = 0.98$ each, graph not shown). The Bland–Altman plots (Bland and Altman 1995) in figures 2 and 3, however, reveal a systematic increase in the apparent plasma volume if the time window exceeds the 5th minute. Furthermore, differences between PV2–5 and PV2–9 (retrospective group 1, figure 2) or PV early and PV late (prospective group 2, figure 3) tend to be related to measured plasma volumes (significant positive correlation in both cases).

In group 1, mean apparent PV2–5 (3104 ± 595 ml) was significantly lower than mean apparent PV2–9 (3452 ± 694 ml), the mean difference being 348 ± 171 ml (11.1 ± 4.6% of PV2–5; $p < 0.05$). In six patients (19%), the apparent PV2–9 exceeded the mean PV2–5 by more than one standard deviation. A PV2–9 smaller than the corresponding PV2–5 was not observed in group 1.

Group 2 revealed a mean apparent PV early (3208 ± 555 ml) that was significantly lower than mean PV late (3592 ± 637 ml) ($p < 0.05$), the difference being 384 ± 131 ml, corresponding to 11.9 ± 3.6% of PV2–5. In two patients (9.5%), apparent PV late exceeded mean PV early by more than 1 standard deviation. A PV late smaller than the corresponding PV early was not observed in group 2.

In one case of each group it was necessary to exclude the first measuring point due to incomplete mixture of dye with blood. No exclusions were necessary, i.e., a complete mixture was reached within 2 min after dye injection, in 97% and 95% of the curves (groups 1 and 2, respectively).

Discussion

The present study demonstrates that extrapolation modalities severely influence the apparent theoretical specific extinction at the time of ICG injection and, thus, the derived PV. Of particular importance are (i) the applied extrapolation technique (mono- or polyexponential) and (ii) the time window for taking measuring points.
Figure 1. The changing kinetic of indocyanine green decay beyond the 5th min after injection, exemplarily demonstrated in a set of measuring points taken from the prospective group 2. $E_{01}$ represents the calculated specific extinction at injection time for the respective group of measuring points. $E_{02}$ (black squares, leading to PV early) represents the first, monoexponential part of dye decay. $E_{02}$ (white triangles, leading to PV late) includes a considerable part of the second, polyexponential kinetic. Nevertheless, $r$-values are 1.0 and 0.99, respectively. The thin full black lines represent the regression lines, the thick full black line represents the cut-off between mono- and polyexponential kinetic. The resulting difference in apparent plasma volumes was about 500 ml in this example. Three black squares are covered by the first three white triangles in this illustration.

Enclosure of measuring points from a time period longer than 5 min after injection of the dye into a monoexponential extrapolation technique results in a significant increase in derived PV. The reason seems to be a change in the kinetic of ICG disappearance from mono- into polyexponential after about the 5th min following injection. This transition, however, occasionally cannot be easily detected especially when using only a few measuring points (figure 1). The impending consequence is a substantial underestimation of the theoretical specific extinction at $t_0$. Investigators of PV should be familiar with this pitfall to avoid such an error.

The phenomenon of a polyexponential kinetic of ICG decay from plasma is not surprising. Several investigators reported the elimination of ICG from plasma to follow a biexponential principle after bolus injection (Buczyński et al 1987, Burns et al 1989, 1991, Grainger et al 1983, Kisor et al 1993, Meijer et al 1988). In two sophisticated investigations in a porcine model, Ott and colleagues suggested a first-order, one-way hepatic uptake and a simultaneously occurring temporary, extrahepatic-extravasal redistribution of ICG to be the reason for this phenomenon (Ott et al 1994, 1996). However, the tested ‘bolus’ in the model (Ott et al 1994) consisted of an infusion over 5 min, and the biexponentially shaped elimination curve...
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**Figure 2.** Bland–Altman plot: differences between two apparent plasma volumes (PV) plotted against their respective average (retrospective group 1; \( n = 31 \)). PV\(_{2-5}\) = apparent plasma volume derived from measuring points taken every 10 s between the 2nd and the 5th min after dye injection. PV\(_{2-9}\) = apparent plasma volume derived from measuring points taken every 10 s between the 2nd and the 9th min after dye injection. Thick full black line is the regression line \((r = 0.58)\), the horizontal thin full black line represents the mean difference, broken black lines are \(\pm 1.96 \times SD\) of this difference.

**Figure 3.** Bland–Altman plot: differences between two apparent plasma volumes (PV) plotted against their respective average (prospective group 2; \( n = 21 \)). PV\(_{early}\) = apparent plasma volume derived from measuring points taken every 20 s between the 2nd and the 5th min after dye injection. PV\(_{late}\) = apparent plasma volume derived from measuring points taken every 60 s between the 3rd and the 7th min after dye injection. Thick full black line is the regression line \((r = 0.63)\), the horizontal thin full black line represents the mean difference, broken black lines are \(\pm 1.96 \times SD\) of this difference.
describes dye decay over 3 h, taking the first sample 7 min after the beginning of dye infusion, i.e., practically at the end of our period of interest.

Our data suggest the dye elimination to be monoexponential over the first few minutes. Furthermore, the kinetic seems to change around minute 5 at least into biexponential, possibly marking that moment when the peripheral compartment is saturated and redistribution back into the plasma begins. Our observations are in total agreement with other investigators having measured ICG decay non-invasively and online using pulse-dye densitometry and who found the period between 2.5 and 5.5 min after recirculation of a bolus (20 mg in 4 ml distilled water) to be most stable for monoexponential extrapolation (Iijima et al. 1998). This was interpreted as a primary ‘fast’ elimination kinetic which changes into biexponentially, replenished by a second, ‘slow’ decay. Thus, the phenomenon of bi- or poly-exponentiality may be the main explanation for an overestimation of PV using the ICG-DT, as observed when combining monoexponential extrapolation and an extended time window (Ishihara et al. 2002, Mi et al. 2003).

There are two possibilities to avoid misinterpretation of PV measurements with ICG-DT: (i) usage of a time window starting beyond the 5th min and applying a biexponential extrapolation technique (Sekimoto et al. 1997), or (ii) usage of a time window ending before the 5th min and applying a monoexponential extrapolation. Which is the better choice for clinical needs?

Sekimoto and co-workers (Sekimoto et al. 1997) measured ICG plasma concentrations in 15 volunteers during the first 30 min after dye injection and compared the PV results from mono- and biexponential regression with different time windows. To be able to perform a biexponential regression analysis to a large time window (5th to 30th min), they applied an ICG dosage four-fold higher (1.0 mg kg$^{-1}$) than we needed to. By ‘computing with a curve-fitting technique’ they found that subjecting data from a time window between the 5th and the 30th min after dye injection to a biexponential analysis leads to the best ‘curve-fitting’ under these conditions. However, a careful look at their PV results reveals that monoexponential extrapolation applied to values derived before the end of the 4th min led to results comparable to those derived from their best biexponential fit. Furthermore, time windows exceeding the 5th min induced an overestimation of PV when a monoexponential regression analysis was applied. This is confirmed by previously provided ‘typical ICG declining curves’ (Haruna et al. 1998, Sekimoto et al. 1997), which also indicate that the ICG decay should be sufficiently described by a monoexponential method within the first 5 min. The argument put forward for a need of biexponential regression of values beyond the 5th min is based on a supposed long mixing time (Haruna et al. 1998, Sekimoto et al. 1997). However, several other authors found, in agreement with us, complete mixing of the dye to be achieved at the latest after 3 min (Bradley and Barr 1968, Busse et al. 1990, Haller et al. 1993, Haneda and Horiuchi 1986, Iijima et al. 1998).

The present work applied a monoexponential extrapolation technique and we found that only measuring points taken before the 5th min after dye injection should be subjected to such extrapolation. The late time window of group 2 showing overestimation was based on previous works, claiming ICG-DT to generally overestimate PV (Ishihara et al. 2002, Mi et al. 2003). Additionally, we found mixing times normally not to exceed the 2nd min. One important reason for this could be our low ICG dosage (0.25 mg kg$^{-1}$) and bolus concentration (2.5 mg ml$^{-1}$). However, there is no need for more dye, since a time window shorter than two half lives is adequate for the determination of PV. In accordance, studies on liver function have shown that this dosage is sufficient to accurately measure the ICG plasma disappearance rate, even when applying a transcutaneous technique (Sakka et al. 2004). By contrast, injecting a four-fold higher dosage with an about three-fold higher concentration (Sekimoto et al. 1997) should
impact the mixing time for physical reasons (e.g., generation of a non-rectangular bolus),
thus limiting the chance of using the short time window for monoexponential extrapolation.
Obviously, higher doses of ICG (Sekimoto et al. 1997) or doses not related to body weight
(Ishihara et al. 2002, Mi et al. 2003) could lead to in calculable kinetics with earlier and
inconstant saturation of the peripheral compartments.

In conclusion, monoexponential analysis of ICG decay in blood provides a rapid and
consistent determination of plasma volume if a time window shorter than 5 min after dye
injection is used. A low ICG dosage offers the advantage of a rectangular bolus with a short
mixing time and provides sufficient extinction for this short time window. In addition, it is
far easier to maintain stable haemodynamics for 5 than for 30 min in a clinical setting and
the results of perioperative PV measurements are of interest immediately, not 30 min later.
Finally, the examiner does not have to take recourse on ‘borrowed’ curve-fitting techniques if
a monoexponential extrapolation technique can be used.

We suggest the following modalities for measurements of PV with ICG by the general
user: (i) inject a small ICG bolus (0.25 mg kg\(^{-1}\) at a concentration of 2.5 mg ml\(^{-1}\)),
(ii) take as many timed samples as possible from the 2nd to the 5th min, (iii) determine
the specific extinction in the samples, (iv) exclude any early values which are ‘not log-linear’
in a monoexponential regression and, finally, (v) extrapolate monoexponentially back to the
specific extinction at injection time to then calculate PV.

Disclosures

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