



# A modified method of measuring plasma volume with indocyanine green: reducing the frequency of blood sampling while maintaining accuracy

Kyung Mi Kim<sup>1</sup> · Do-Yang Park<sup>1</sup> · Eun-Hwa Kang<sup>2</sup> · Myojung Kim<sup>1</sup> · Byung-Moon Choi<sup>1</sup> · Gyu-Jeong Noh<sup>3</sup> · Eun-Kyung Lee<sup>2</sup>

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## Abstract

Among various methods for measuring the plasma volume (PV), the indocyanine green (ICG) dilution technique is a relatively less invasive method. However, the ICG method is rather cumbersome because 10 blood samples need to be obtained within a short time after ICG administration. Thus, reducing the frequency of blood sampling while maintaining the accuracy would facilitate plasma volume measurement in clinical situations. We here developed a modified method to measure plasma volume using 2260 ICG plasma concentration data from 115 surgical patients. The mean relative error (MRE) and the percentage of cases with relative error (RE) greater than 5% in total (PRE) were used to quantify the difference between plasma volumes obtained by the original and modified methods. RE was determined as follows.  $RE(\%) = (PV_{\text{obtained by original method}} - PV_{\text{obtained by modified method}}) / PV_{\text{original}} \times 100$ .  $PV_{\text{modified}}$  was assumed to be equal to  $PV_{\text{original}}$  when the RE was < 5%. When the number of samples selected for the plasma volume estimation was 4 or less, the PRE was mostly 10% or more. Five out of the 10 blood samples (order: 1st, 2nd, 3rd, 9th, and 10th) showed similar accuracies with the plasma volume obtained by the original method (original:  $2.72 \pm 0.64$  l, modified:  $2.72 \pm 0.65$  l). This modified method may be able to aptly replace the original method and lead to a wider clinical application of the ICG dilution technique. Further validation is needed to determine if the results of this study may be applied in other populations.

**Keywords** Accuracy · Indocyanine green · Measurement · Plasma volume

Byung-Moon Choi and Eun-Kyung Lee contributed equally to this work as corresponding authors.

✉ Byung-Moon Choi  
byungmoonchoi7@gmail.com

✉ Eun-Kyung Lee  
lee.eunk@ewha.ac.kr

Kyung Mi Kim  
sumsonyo@gmail.com

Do-Yang Park  
carusgigle@gmail.com

Eun-Hwa Kang  
eun\_hwa96@ewhain.net

Myojung Kim  
rlaaywd@hanmail.net

Gyu-Jeong Noh  
nohgi@amc.seoul.kr

## 1 Introduction

Maintaining euvolemia in patients is of critical clinical importance, because hypovolemia leads to hypotension or tachycardia, and hypervolemia due to fluid overdose leads to tissue edema or respiratory compromise [1]. Therefore,

<sup>1</sup> Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

<sup>2</sup> Department of Statistics, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul 03760, Korea

<sup>3</sup> Departments of Anaesthesiology and Pain Medicine, Clinical Pharmacology and Therapeutics, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, Korea

various efforts have been made to properly maintain the blood volume of patients; unfortunately, no commercial equipment has yet been developed to monitor the plasma volume in real-time.

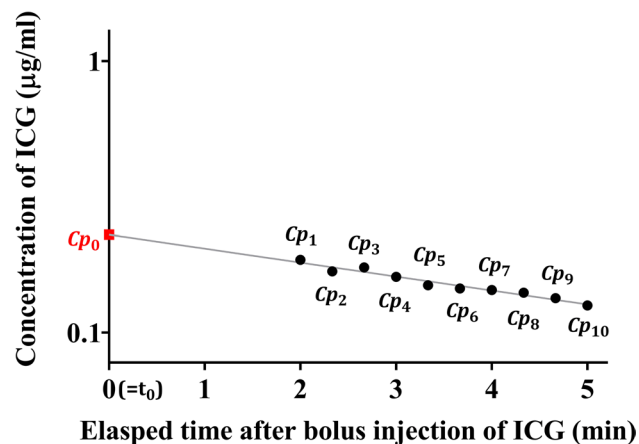
The indocyanine green (ICG) dilution technique has been used to measure the plasma volume (Fig. 1), but the method is quite cumbersome because it requires a total of 10 blood samplings every 20 s for 3 min [2]. If the frequency of blood collection can be reduced, the ICG dilution technique may be applied in a wider range of clinical settings. In our previous study, plasma volumes of 118 surgical patients were measured before and after surgery using the original ICG dilution technique [3]. Using these plasma volume data, we sought to develop a modified method that requires fewer blood samplings for producing comparable measurements.

In this study, we aimed to determine how many blood samples can be reduced using the existing plasma volume measurement data. Moreover, we tried to identify the order in which blood samples should be drawn within the same frequency of blood collection that allows for maximum accuracy.

## 2 Material and methods

### 2.1 Source of plasma volume measurement data

In order to modify the existing ICG dilution technique, we utilized the data related to plasma volume measurement from



**Fig. 1** Estimation of plasma volume using the original indocyanine green (ICG) dilution technique.  $C_{p0}$  indicates the theoretical concentration at  $t_0$  (time of ICG administration). The concentration was derived from mono-exponential extrapolation of concentrations using 10 samples obtained from 2 to 5 min of ICG administration. Each sample was taken at 20-s intervals. Ten samples were named from  $C_{p1}$  to  $C_{p10}$ . For example,  $C_{p1}$  and  $C_{p10}$  indicate plasma concentration at 2 and 5 min after the administration of ICG, respectively. The solid grey line represents the regression line between the 10 plasma concentrations from  $C_{p1}$  to  $C_{p10}$

a previous study [3]. The previous study was approved by the institutional review board (IRB) of Asan Medical Center (#2012-0169) and registered on an international clinical trials registry platform (<https://cris.nih.go.kr>; KCT0001788) (Minerva Anesthesiol. 2019, <https://doi.org/10.23736/S0375-9393.19.13952-1>). This current study was approved as a retrospective study by the IRB of Asan Medical Center (#2020-0631). Induction and maintenance of anesthesia were achieved in accordance with the institution's standard operating procedure [3]. Before the induction of anesthesia, a 20-gauge catheter was inserted in a radial artery for frequent blood sampling. In the contralateral arm, a 16-gauge angiocatheter was placed in the antecubital vein for ICG injection. Plasma volume was measured before and after surgery. Preoperative measurements were performed before the induction of anesthesia, and postoperative measurements were performed before transfer to the post-anesthesia care unit. Briefly, the original ICG dilution technique for plasma volume measurement is as follows [3]. ICG powder (25 g) was dissolved in 10 ml distilled water. ICG diluted to 2.5 mg/ml was prepared in a 10 ml syringe. ICG (0.25 mg/kg) was given to each patient as quickly as possible. Two minutes after injection of ICG, 3 ml of arterial blood was sampled using a heparinized syringe every 20 s for 3 min (10 samples total). After separation of plasma by centrifuging for 10 min at 3,500 rpm, the absorbance of the plasma sample at 805 nm was measured using a spectrophotometer (Double beam spectrophotometer U-2900®, Hitachi High-Technologies Global, Tokyo, Japan). Plasma ICG concentrations were estimated using calibration standard curves constructed from ICG solutions prepared to cover a plasma concentration of 0–1 mg/dl. Calibration standard curves were constructed every two weeks, except for periods when there was no patient enrollment. A total of 24 calibration standard curves were obtained throughout the study period, and the coefficient of determination ( $R^2$ ) ranged from 0.997 to 1.000. The measured ICG concentrations were plotted on a semilogarithmic graph. The resulting regression line was extrapolated to  $t_0$  (time of ICG administration) at the end of administration, and this theoretical concentration of ICG concentration at  $t_0$  ( $C_{p0}$ ) was used to calculate the plasma volume. Plasma volume was calculated by dividing ICG amount by  $C_{p0}$  (Eq. 1).

$$\text{Plasma volume (L)} = \frac{\text{ICG amount administered (mg)}}{C_{p0} (\mu\text{g/ml})} \quad (1)$$

### 2.2 Statistical analysis

Statistical analysis was performed using the 236 plasma estimates obtained from 118 patients before and after surgery [3]. If the absolute value of the correlation coefficient

between 10 ICG concentrations used to estimate one plasma volume on a semilogarithmic graph was lower than 0.9, it was considered an outlier and excluded from the analysis. In general, the correlation coefficient of the standard curve is higher than 0.95 [3, 4]. Ten of the 236 cases were excluded from the analysis (median absolute correlation coefficient: 0.82). A total of 2,260 plasma concentration data (10 plasma samples per plasma volume measurement × 226 cases) were included in the analysis.

For convenience, 10 plasma samples were named in order from  $Cp_1$  to  $Cp_{10}$ . For example,  $Cp_1$  and  $Cp_4$  refer to plasma concentrations at 2 and 3 min after ICG administration, respectively. The original plasma volume ( $PV_{original}$ ) value calculated using all 10 plasma concentrations were considered as the true value. Plasma volume estimated by reducing the number of samples with various combinations was considered as the modified plasma volume ( $PV_{modified}$ ). Table 1 shows the possible number of combinations with which  $PV_{modified}$  can be calculated; in total, there were 1,012 possible combinations. To define the difference between  $PV_{modified}$  and  $PV_{original}$ , the relative error (RE) was calculated for each combination as follows.

$$RE_{i,j}(\%) = \left| \frac{PV_{original,i} - PV_{modified,i,j}}{PV_{original,i}} \right| \times 100, \quad (2)$$

$i = 1, 2, \dots, 226, j = 1, 2, \dots, 1012$

where  $PV_{original,i}$  is the  $PV_{original}$  of the  $i$ th case and  $PV_{modified,i,j}$  is the  $PV_{modified}$  of the  $i$ th case at the  $j$ th combination. There was a total of 228,712 REs (226 cases × 1012 combinations). If RE was less than 5%,  $PV_{modified}$  was assumed to be equal to  $PV_{original}$ ; this means that if  $RE_{i,j}$  is greater than 5%, the plasma volume of the  $i$ th case at  $j$ th combination is clinically different from the original plasma volume, and the  $i$ th case of the  $j$ th combination is not suitable for substituting of the original ICG dilution technique.

Two parameters—the mean relative error (MRE) and the percentage of cases with RE (PRE) greater than 5% out of 226 in total—were used to quantify the degree of the difference between  $PV_{modified}$  and  $PV_{original}$  at each combination. MRE and PRE were defined as follows.

$$MRE_j = \frac{\sum_{i=1}^{226} RE_i}{226}, j = 1, 2, \dots, 1012$$

$$PRE_j = \frac{\text{Number of REs greater than 5\%}}{226} \times 100, j = 1, 2, \dots, 1012 \quad (3)$$

where  $MRE_j$  and  $PRE_j$  are MRE and PRE at the  $j$ th combination, respectively. The smaller the MRE and PRE values, the more likely it is to replace the original ICG dilution technique.

Based on the following three principles, we found a modified method that can replace the original method. First,  $PV_{modified}$  should not be clinically different from  $PV_{original}$ . Second, MRE and PRE should be as small as possible. Third, if the MRE and PRE are clinically similar, the combination with the smallest number of samples used to estimate the plasma volume is chosen.

Data are expressed as mean ± standard deviation for normally distributed continuous variables, median (25–75%) for non-normally distributed continuous variables, or count and percentage for categorical variables.

### 3 Results

A total of 2260 (226 cases × 10 concentrations/case) ICG plasma concentration data from 115 patients were analyzed. The physical characteristics of these patients are shown in Table 2. In the 226 cases, the median (25–75%) absolute value of correlation coefficient between 10 ICG concentrations used to estimate one plasma volume on a logarithm plot was 0.99 (0.98–1.0). The distributions of

**Table 1** Combination of plasma sample selections available for plasma volume estimation

Number of samples included in the analysis	Number of possible combinations	Examples
2	${}_{10}C_2 = 45$	( $Cp_1, Cp_2$ ), ( $Cp_9, Cp_{10}$ )
3	${}_{10}C_3 = 120$	( $Cp_1, Cp_2, Cp_3$ ), ( $Cp_8, Cp_9, Cp_{10}$ )
4	${}_{10}C_4 = 210$	( $Cp_1, Cp_2, Cp_3, Cp_4$ )
5	${}_{10}C_5 = 252$	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_5$ )
6	${}_{10}C_6 = 210$	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_5, Cp_6$ )
7	${}_{10}C_7 = 120$	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_5, Cp_6, Cp_7$ )
8	${}_{10}C_8 = 45$	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_5, Cp_6, Cp_7, Cp_8$ )
9	${}_{10}C_9 = 10$	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_5, Cp_6, Cp_7, Cp_8, Cp_9$ )

Based on the indocyanine green (ICG) dilution technique for plasma volume measurement, arterial blood was sampled every 20 s for three minutes (10 samples total) starting from two minutes after the injection of 0.25 mg/kg ICG. For convenience of analysis, 10 samples were named as  $Cp_1$  to  $Cp_{10}$ . For example,  $Cp_1$  and  $Cp_4$  indicate the plasma concentrations at 2 and 3 min after ICG administration, respectively

MRE and PRE in combinations of sample selection for plasma volume estimation are depicted in Fig. 2. As the number of samples selected for plasma volume estimation was increased, the variation of MREs decreased. When nine plasma concentrations were selected, all MREs were less than 5%. Also, the smallest MRE among the combinations of the selected sample numbers gradually decreased as the number of samples included in the plasma volume estimation was increased. On the other hand, the minimum PRE in each combination was 10% or more until four plasma samples were selected, whereas the minimum PRE was at most 1% when selecting five or more plasma samples. Although the plasma volume was estimated using the same number of plasma samples, high variability of MRE and PRE was observed, indicating that the order of samples included in the estimation is also important.

Table 3 shows the combinations with the minimum MRE and PRE for each sample number selected. By taking into account Fig. 2 and Table 3, it was possible to select five plasma samples out of ten, and the order was 1st, 2nd, 3rd, 9th, and 10th. In other words, the first three plasma samples and the latter two plasma sample data could yield similar plasma volume results with the original method in terms of accuracy. The mean  $\pm$  SD plasma volumes obtained from the original and modified methods were  $2.72 \pm 0.64$  and  $2.72 \pm 0.65$ , respectively. The plasma volumes obtained by the original method and the modified method are presented

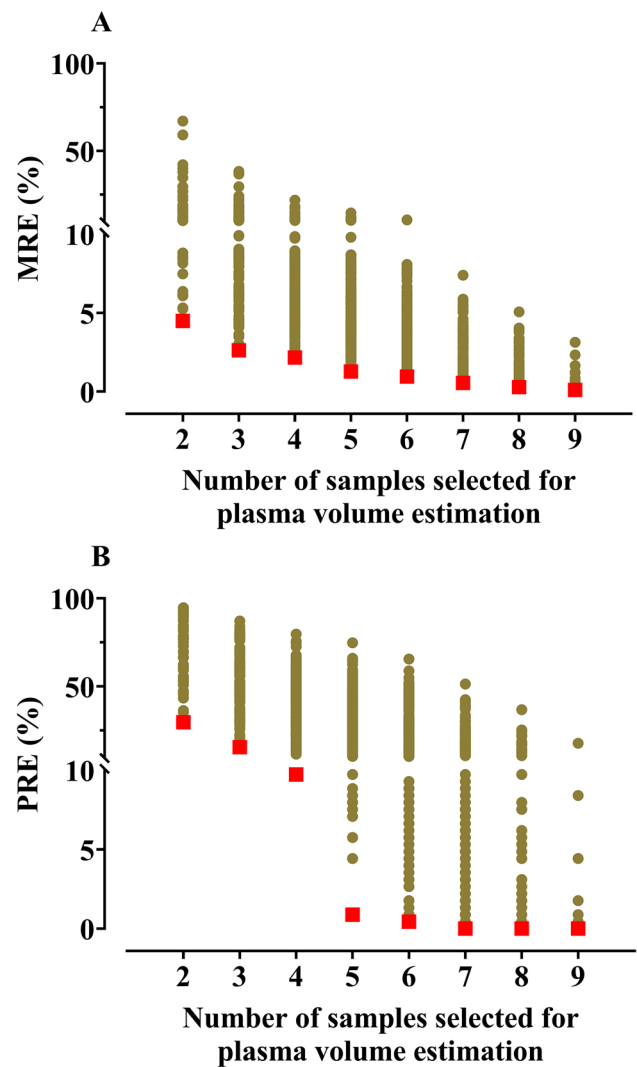
**Table 2** Characteristics of patients included in the analysis (N=115)

Age, year	57 $\pm$ 10
Weight, kg	64.3 $\pm$ 9.5
Height, cm	164.9 $\pm$ 8.0
Male/female	84/31
ASA PS 1/2	32/83
EF, %	62 $\pm$ 4
Duration of operation, h	2.8 (2.3–3.1)
Intraoperative parameters related to plasma volume	
Ringer's lactate, ml	500 (459–552)
Colloid, ml	500 (400–750)
Urine output, ml	125 (70–198)
Patients requiring transfusion, n	2
EBL, ml	128 (90–190)
Type of surgery	
Stomach	75 (65.2)
Colorectal	40 (34.8)

Data are presented as mean  $\pm$  SD, median (25–75%), or count (%), as appropriate

Colloid: Volulyte® (6% hydroxyethyl starch 130/0.4, Fresenius Kabi AG, Bad Homburg, Germany)

ASA PS American Society of Anesthesiologists Physical Status, EF ejection fraction measured using echocardiography, EBL estimated blood loss



**Fig. 2** Distribution of the mean residual error (MRE, **A**) and percentage of cases with relative errors greater than 5% out of 226 (PRE, **B**) in the combinations of sample selection for plasma volume estimation. Gold circles indicate MRE or PRE in each combination (total number of combinations: 1012). Red squares represent the smallest MRE or PRE value in the combination of the number of samples selected

in Fig. 3. In almost all cases, the fold change of the plasma volume obtained by the modified method with respect to the plasma volume obtained by the original method was between 5%.

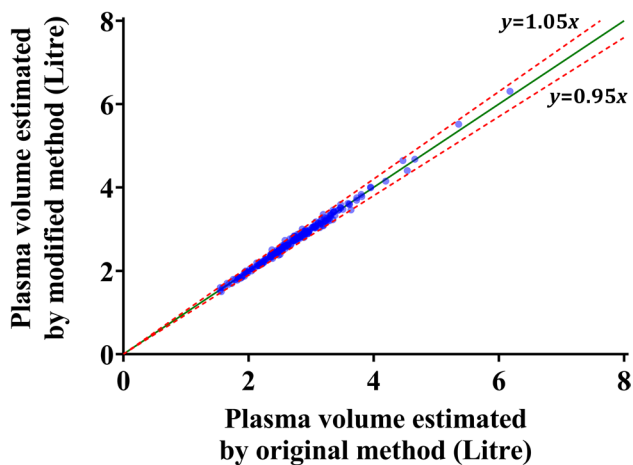
## 4 Discussion

In this study, we developed a modified ICG dilution method to replace the original technique for estimating plasma volume. Five out of the 10 blood samples showed similar accuracies with the plasma volume obtained by the original

**Table 3** Combinations with the minimum values of MRE and PRE for each sample number selected

Number of samples included in the analysis	Combination of sample selections with the smallest MRE and PRE	MRE	PRE
2	( $Cp_2, Cp_{10}$ )	4.492	29.646
3	( $Cp_1, Cp_2, Cp_{10}$ )	2.625	15.487
4	( $Cp_1, Cp_2, Cp_9, Cp_{10}$ )	2.162	9.735
5	( $Cp_1, Cp_2, Cp_3, Cp_9, Cp_{10}$ )	1.280	0.885
6	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_9, Cp_{10}$ )	0.956	0.442
7	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_8, Cp_9, Cp_{10}$ )	0.551	0.000
8	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_6, Cp_8, Cp_9, Cp_{10}$ )	0.518	0.000
9	( $Cp_1, Cp_2, Cp_3, Cp_4, Cp_5, Cp_7, Cp_8, Cp_9, Cp_{10}$ )	0.106	0.000

Based on the indocyanine green (ICG) dilution technique for plasma volume measurement, arterial blood was sampled every 20 s for three minutes (10 samples total) starting from two minutes after the injection of 0.25 mg/kg ICG. For the convenience of analysis, 10 samples were named as  $Cp_1$  to  $Cp_{10}$ . For example,  $Cp_1$  and  $Cp_4$  indicate the plasma concentrations at 2 and 3 min after ICG administration, respectively. MRE, mean residual error; PRE, percentage of cases with relative errors greater than 5% out of 226



**Fig. 3** Plasma volume estimated by the original and modified methods. The solid green line represents the line of identity ( $y=x$ ). The modified method used a total of five plasma concentrations at the 1st ( $Cp_1$ ), 2nd ( $Cp_2$ ), 3rd ( $Cp_3$ ), 9th ( $Cp_9$ ), and 10th ( $Cp_{10}$ ) time points

method. Of the 10 previous blood samples, the order of the selected samples was 1st, 2nd, 3rd, 9th, and 10th.

It would be beneficial to monitor the blood or plasma volume during fluid therapy. Radio-iodinated serum albumin and Evans blue have been used as tracers to measure the blood or plasma volume [5, 6]. However, these tracers do not allow for making measurements in short intervals due to radioactivity contamination or dye accumulation [7]. ICG is a cyanine dye used in determining the hepatic function and the blood flow in the liver and stomach [8]; ICG tightly binds to plasma proteins and becomes confined to the vascular system, and can thus be reliably used to measure blood or plasma volume. The estimated volume of distribution of ICG is the blood or plasma volume, and the blood volume can be converted to plasma volume using the hematocrit value [2]. Importantly, ICG has a short elimination half-life

(approximately 4.7–5 min) [8], and thus has the advantage of being able to repeat plasma volume measurement in short intervals. Despite these characteristics of ICG, clinical application of the ICG dilution technique is still limited due to the complicated process of blood sampling and quantitation of ICG plasma concentration in the laboratory [7]. If the inconvenience of frequent blood collection can be reduced, the ICG dilution technique may be applied in a wider range of clinical settings.

In addition to the methods used in the current study, there are other methods for measuring blood volume. The pulmonary blood volume and circulating blood volume can be measured using the transpulmonary dye dilution method [9]. Since ICG was injected into the right atrium, it is necessary to insert a central venous catheter [9]. Blood volume can also be measured using commercialized PiCCO (Philips IntelliVue MP40 with PiCCO-technology module Philips Healthcare, Cleveland, Ohio, USA), which is a comparatively less invasive method than the pulmonary artery catheter [10]. However, an arterial catheter is placed in the descending artery via the femoral artery in this method [11]. An ultrasound dilution technology can measure the blood volume in critically ill patients by using an extracorporeal arteriovenous loop approach [12]. However, this method is more invasive than the method used in the current study.

The elimination pattern of ICG shows mono-exponential decay during the first 5 min after recirculation and then changes to biexponential decay [8, 13]. Therefore, ICG concentrations for 2 to 5 min after administration theoretically form a straight line by logarithmic conversion; in practice, however, the plasma concentrations of ICG obtained from biological samples do not form a perfectly straight line. Therefore, in order to correctly estimate the  $Cp_0$ , 10 blood samples were taken in the original method. In this current study, when MRE and PRE were considered, we observed that the number of blood sampling of the original method

could be reduced in half. A recent study on plasma volume measurement using ICG found that plasma volume can be accurately measured with only five samples [4]; unfortunately, no comparisons were made with the plasma volumes obtained with the original method. The authors argued that randomly selected five blood samples without specific evidence well-explained the decay curve of plasma ICG concentrations. The time point of blood sampling presented by the authors was to collect blood at an interval of 45 s, evenly dividing the 180 s from 2 to 5 min after the administration of ICG. However, as shown in Fig. 2, even with five samplings, the MRE and PRE differed greatly depending on how the order is determined. When the 1st, 3rd, 5th, 7th, and 9th blood sampling combination was selected, the MRE and PRE were 4.4% and 23.3%, respectively. In order to increase the accuracy of plasma volume measurement, the first and the last samples of the 10 samples had to be included, which is in line with previous knowledge that the points at both ends are generally more influential than those in the middle in linear regression [14].

As of yet, there are no clear criteria as to how much difference is to be regarded as the same value when the plasma volume is measured by two different methods. In this study, based on general statistical concepts, the plasma values obtained by the two methods were considered equal when the relative error was less than 5%. When the 1st, 2nd, 3rd, 9th, and 10th blood sampling combination were selected, the mean relative error was 1.3%, which is smaller than the 2.5% accuracy when measuring blood volume with the albumin I-131 kit [15].

The Shiny web application was further developed for the convenience in measuring the plasma volume by the ICG dilution technique (<https://ek-lee.shinyapps.io/ICGtechnique/>, Inventors: Eun-Hwa Kang and Eun-Kyung Lee). The application was configured to choose between the original method and the modified method, and by entering the ICG dose and concentrations, the  $Cp_0$  and plasma volume results can be obtained. The blood collection time is already entered as a default value but can be modified.

There are some limitations to this study. First, the actual time of blood sampling did not exactly match the target time. Blood collection had to be carried out every 20 s from 2 to 5 min after ICG administration, which made it difficult to accurately keep the preset time. Nevertheless, there were no more than 10-s delays beyond the scheduled time, so the analysis was performed according to the order of blood sampling. Second, further validation is needed to determine if the results of this study may be applied in other populations including children. In general, a newly developed method needs to be validated in various populations, but the modified method has yet to be fully validated. Nevertheless, the current results may be considered as the most reliable data on this topic to date because the study included

a large number of adults (N = 115) with various physical characteristics.

In conclusion, our newly proposed modified ICG dilution method achieved comparable results with the original method while using only 5 out of the 10 originally needed number of blood samples. Of the 10 blood samples, the order of the 5 selected samples was 1st, 2nd, 3rd, 9th, and 10th. We expect that this modified method may be able to aptly replace the original method and lead to a wider clinical application of the ICG dilution technique for plasma volume measurement.

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## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

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