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Determination of the standard value of circulating blood volume during anesthesia using pulse dye-densitometry: a multicenter study in Japan

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Abstract
Purpose. The standard value for circulating blood volume (BV) during anesthesia was determined by a multicenter study in Japan. The significance of BV on the reduction of blood pressure after the induction of anesthesia was also examined.
Methods. The study included 184 patients from eight university hospitals. After the induction of anesthesia, pulse dye-densitometry was performed according to a uniform protocol. Factors contributing to reduced blood pressure after induction of anesthesia were examined by multiple logistic regression analysis.
Results. The mean and standard deviation of BV was 80.0 ± 13.9 ml·kg^{-1}; for females and 84.2 ± 15.3 ml·kg^{-1} for males ($P >$ 0.05). There was no age difference in terms of BV. After adjusting for the effects of height, weight, and age, the factors predisposing to a reduction in blood pressure of >20 mmHg after induction of anesthesia were found to be age ($P < 0.01$) and BV (ml·kg^{-1}) ($P < 0.001$).
Conclusion. We determined the BV of anesthetized patients before surgery in Japan using pulse dye-densitometry. It is suggested that age is not a factor regarding BV, and that blood pressure tends to be reduced in hypovolemic patients after induction of anesthesia.

Key words Blood volume · Pulse dye-densitometry · Multicenter study · Hemodynamics

Introduction

The status of the circulating blood volume (BV) is a preoperative concern for the anesthetist. The values have been estimated indirectly using preload parameters, or individual perioperative medical records, or both. The contribution of BV to hemodynamics has not yet been determined based on clinical evidence, although one of the most important tasks of an anesthetist is to optimize BV status.

Pulse dye-densitometry (PDD) was recently developed to monitor BV at the bedside [1–3]. This monitor is based on a dilution technique in which a widely used dye, indocyanine green (ICG), is injected as a bolus intravenously. The breakthrough associated with this technique is the less invasive measurement of the ICG concentration, rendering bedside monitoring possible.

There is accumulating clinical evidence regarding the means by which BV can be manipulated [4]. Although this technique is now in clinical use, the standard reference values have not been determined, and the physiological properties of BV remain unknown. To begin a clinical study of BV, a basic data set must first be constructed; otherwise, it would not be possible to evaluate any information obtained clinically. We designed a uniform protocol to be tested at eight university hospitals to determine the intraoperative value of the BV. We also explored whether the BV value is significant in terms of hemodynamic management.

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Materials and methods

The uniform protocol was approved by each university's ethics committee. Written informed consent was obtained from all enrolled patients ($n = 184$). The following patients were excluded from the study: emergency cases, patients who were undergoing intravenous alimentation, patients with a physical status exceeding American Society of Anesthesiologists (ASA) 3, and afternoon cases.

Procedure

Preoperative infusion was limited to less than 300 ml of electrolyte solution. All patients were fasted overnight. After noninvasively measuring the blood pressure and heart rate, anesthesia was induced by thiopental ($5\,mg \cdot kg^{-1}$) or propofol ($2\,mg \cdot kg^{-1}$), and fentanyl (100 µg); the anesthesia was maintained using nitrous oxide (50%–66%) and sevoflurane (1%). Blood pressure was repeatedly measured every 5.0 or 2.5 min. The lowest values of systolic and diastolic blood pressure after induction of anesthesia were recorded.

Central blood volume (CBV) and cardiac output (CO) were measured using (PDD) (DDG analyzer; Nihon Kohden, Tokyo, Japan) before the surgery began. The measurement was initiated promptly after the hemodynamics was stabilized, and it took approximately 6 min to complete the measurement using a nose probe. The pulsation of the artery, obtained by the probe, was confirmed to be as high as could be measured by PDD (i.e., >1.0 on the pulsation scale). An arterial catheter was inserted into a radial artery, and a blood sample for measuring hemoglobin was obtained.

The theoretical background on which PDD is based has been described previously [1]. Validations of the obtained values, compared with radioisotope measurements, are also provided in previous reports [2,3]. ICG 20 mg diluted with 4–5 ml of distilled water was injected into the patient followed by flushing with 20 ml of saline, which was used to draw the dye-densitogram. The arterial ICG concentration was measured continuously from the probe attached to the nostril. The BV value was calculated from the obtained dye-densitogram. Each record was sent to the organizer (T.I.) of this study, and the quality of the dye densitogram was assessed. The following inappropriate recordings were excluded: a distorted late decay curve and a decay curve unfitted to a semilogarithmic scale. Because the diluted concentration of ICG is obtained from the decay curve, the curve should be fitted to a straight line on the semilogarithmic scale to obtain precise values.

Statistical analysis

The significant differences with respect to gender and age group (each 20 years) were analyzed using Student's *t*-test or analysis of variance (ANOVA). Height and weight were used for the regression equation for the prediction of BV according to methods described in previous articles [5].

For the present analysis, patient age, weight, height, and BV were treated as continuous variables, and gender was treated as a categorical variable. For each characteristic, a simple logistic regression model was used to assess the univariate association of the given characteristic with a reduction in systolic blood pressure (BP) of more than 20 mmHg. Variables that reached the $P < 0.05$ level of significance on the univariate analysis were retained for multivariate analysis. A multiple logistic regression model with stepwise elimination of nonsignificant factors was then used to identify a set of independent factors contributing to BP reduction. The odds ratio for a BP reduction of >20 mmHg was calculated for each variable. $P < 0.05$ was considered significant. All analyses were performed with the use of the software package JUSE-MA V4.5 plus (The Institute of the Japanese Union of Scientists & Engineers, Tokyo, Japan).

Results

Basic statistical data

We gathered the data from 184 subjects and examined the appropriateness of the dye-densitogram. Twelve data sets were dropped because of distorted DDG or DDG unfit for the semilog scale. The height, weight, and diastolic BP of females were significantly lower than those of the males (Table 1), and the cardiac index (CI) of the females was significantly higher than that of the males (Table 2). The mean BV was higher for males than for females, although no statistical significant dif-

Table 1. Background of the patients

Sex	No.	Age (years)	Height (cm)	Weight (kg)	sysBP (mmHg)	diaBP (mmHg)	HR (/min)
Male	92	44.5 ± 20.9	169.0 ± 6.9	63.1 ± 10.8	127.8 ± 20.6	74.8 ± 13.7	75.2 ± 15.7
Female	80	41.5 ± 18.1	157.0 ± 6.8*	54.2 ± 8.6*	123.3 ± 21.4	60.8 ± 13.7*	79.6 ± 14.1

sysBP, systolic blood pressure; diaBP, diastolic blood pressure; HR, heart rate
* $P < 0.05$, indicating a significant difference between groups

Table 2. Basic data obtained from pulse dye-densitometry

Sex	CO (l/min)	CI (l/min/m^2)	K (/min)	BV (l)	BV (ml/kg)	CBV (l)
Male	4.5 ± 1.5	2.6 ± 0.8	0.17 ± 0.06	5.3 ± 1.2	84.2 ± 15.3	1.8 ± 0.7
Female	4.6 ± 1.7	3.1 ± 1.1*	0.20 ± 0.04*	4.3 ± 0.8*	80.0 ± 13.9	1.7 ± 0.5
All	4.6 ± 1.6	2.8 ± 1.0	0.19 ± 0.06	4.8 ± 1.1	82.3 ± 14.8	1.8 ± 0.6

CO, cardiac output; CI, cardiac index; K, hepatic dye clearance rate; BV, circulating blood volume; CBV, central blood volume calculated from CO multiplied by the mean transit time of the first circulation of the dye
* $P < 0.05$, indicating a significant difference between genders

Table 3. Reduction of blood pressure after induction of anesthesia

Time	sysBP (mmHg)	diaBP (mmHg)	HR (/min)
Preinduction	125.7 ± 21.1	72.0 ± 14.0	77 ± 15
Postinduction	104.0 ± 13.1*	60.5 ± 12.5*	72 ± 15

* $P < 0.05$ between preinduction and postinduction of anesthesia

ference was found ($P > 0.05$) (Table 2). We found no age-dependent difference in the BV (Table 1). We also found no significant difference in the BV between the induction agent groups (79.7 ± 15.0 ml·kg^{-1} for propofol ($n = 53$) and 83.5 ± 14.6 ml·kg^{-1} for thiopental ($n = 119$); $P = 0.118$).

Linear regression equation to predict BV

The linear regressions of the BV were as follows.

BV (liters) = $0.700H^3 + 0.042W - 0.691$ (males)
BV (liters) = $0.075H^3 + 0.038W + 2.002$ (females)

where W is the weight in kilograms, and H is the height in meters. For the predication of BV, H^3 and W were significant factors ($P < 0.01$) for males, which was statistically confirmed by the multilinear regression model. For females, W was a significant factor ($P < 0.001$), but H^3 was not ($P > 0.05$).

Reduction of blood pressure after induction of anesthesia

After the induction of anesthesia, the systolic blood pressure and heart rate significantly decreased ($P < 0.01$) (Table 3). Age, weight, and BV were found to be significant contributing factors with respect to a reduction in BP (Table 4). The odds ratios used to predict blood pressure reduction were low BV (less than the mean –1.96 SD, 54 ml·kg^{-1}) and age group (70–89 years old) (Table 5). We thus found BV-dependent BP reduction (Fig. 1). Multiple logistic regression analysis showed that BV ($P = 0.00013$), age ($P = 0.0023$), and weight ($P = 0.034$) were contributing factors for BP reduction after induction of anesthesia.

Table 4. Characteristics assessed as potential predictors of a reduction in systolic blood pressure of >20 mmHg after induction of anesthesia

Characteristics	No.	*P*
Sex		0.134
Male	92	
Female	80	
Age (years)		0.0002
10–29	55	
30–49	51	
50–69	47	
70–89	19	
Height (cm)	172	0.086
Weight (kg)		0.003
≤50	30	
50–75	134	
≥76	8	
Blood volume		0.032
≤ mean – 1.96 SD	6	
mean ± 1.96 SD	160	
≥ mean + 1.96 SD	6	

P values were obtained from logistic regression assessing the univariate association of the given characteristic for more than 20 mmHg reduction of systolic BP after induction of anesthesia

Table 5. Multivariate analysis of a reduction in systolic blood pressure of >20 mmHg after induction of anesthesia

Characteristics	OR	95% CI	*P*
Sex			0.733
Male	1	—	
Female	1.04	0.53–1.74	
Age (years)			0.0023
10–29	1	—	
30–49	1.33	0.61–2.89	
50–69	3.14	1.39–7.07	
70–89	3.51	1.16–10.64	
Weight (kg)			0.034
≤50	0.53	0.23–1.20	
50–75	1	—	
≥75	2.00	0.66–6.09	
Blood volume			0.00013
≤ mean – 1.96 SD	4.76	0.54–41.63	
mean ± 1.96 SD	1	—	
≥ mean + 1.96 SD	0.19	0.02–1.67	

OR, odds ratio; CI, confidence internal
Odds ratio was calculated on the basis of the parameter coefficients from the logistic regression analysis. Significance levels were determined by the χ^2 test

Table 6. Previous studies of quantitative estimation of circulating blood volume

Study	Method	Males (ml/kg)	Females (ml/kg)
Gibson and Evans (1937) [6]	Evans blue	77.7	66.1
Von Porat (1951) [7]	Evans blue	81.6	74.3
Peden et al. (1960) [8]	RBC	68.9 (both genders)	
	RISA	77.1 (both genders)	
Albert (1963) [9]	RISA	66.2	60.7
Ogawa et al. (1970) [10]	RISA	72.4	67.8
Shintani (1986) [11]	ICG (blood sampling)	90.9 ± 19.1 (n = 193)	93.4 ± 17.8 (n = 156)
Our study (2003)	ICG (PDD)	84.2 ± 15.3 (n = 92)	80.0 ± 13.9 (n = 80)

RBC, ^{51}Cr-labeled red blood cell method; RISA, ^{131}I human serum albumin method; ICG, indocyanine green; PDD, pulse dye-densitometry

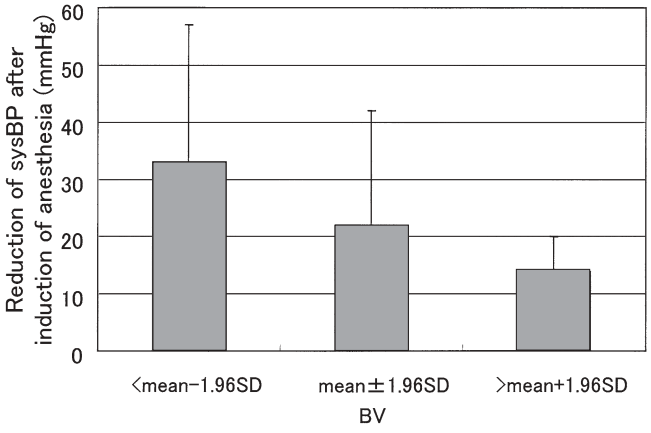

Fig. 1. Blood volume-dependent reduction in blood pressure (*BP*) after the induction of anesthesia. Multiple logistic regression analysis confirmed a significant contribution of blood volume (*BV*) to a reduction in BP after induction of anesthesia ($P < 0.001$; the data were treated as continuous volumes)

Discussion

Standard values and distribution of BV

We demonstrated the Japanese standard value of BV during anesthesia. The BV values were 84.2 ± 15.3 ml·kg^{-1} for males and 80.0 ± 13.9 ml·kg^{-1} for females. Although we failed to find statistical significant difference, the female BV was lower than the male BV, as previous studies have also reported (Table 6). Interestingly, there was no age difference for the BV value. We also provided an estimation formula for predicting BV, although this estimation should be used carefully because there is large variation among individuals.

Comparison of values with historical studies

Over the years, the standard BV value has been examined at a number of institutions using different tracers (Table 6) [6–11]. The mean BV value has varied among studies. However, the tendency appears to be that the ICG distribution volume is larger than that found with ^{131}I or ^{51}Cr. Kisch et al. reported that the difference between the BV measured by Evans blue and the BV measured by ICG sampling methods was 3.5% (calculated by our group) [12]; therefore, the two values should be considered identical. Meanwhile, the BV estimated using an isotope approach seems to be substantially lower than the BV estimated by ICG. Previous validation studies conducted using both PDD and ^{131}I have demonstrated that BV-PDD was slightly higher (3.99% ± 10.54%) than BV-^{131}I [3]. One other validation study compared BV-PDD and BV using ^{51}Cr-labeled red blood cells, which may have been a more reliable approach because red blood cells are unlikely to leak from the intravascular space [13], revealing that a BV-PDD was 4.2% ± 4.9% higher than BV-^{51}Cr. Considering these results, it appears that BV-PDD slightly (approximately 4%) overestimates the BV value measured by radioisotope.

Mi et al. demonstrated that BV increased by approximately 15% after the induction of anesthesia [14]; this mechanism of BV expansion by anesthesia itself may explain the higher BV value obtained in our study than that reported in previous studies. Because we wanted to use this standard value during anesthesia, and the condition of the patients may differ from that of normal healthy volunteers (as patients must fast before surgery), we decided to measure BV during anesthesia. The present value should thus be considered the standard value during anesthesia in the Japanese population.

In four of five previous studies, the value obtained for females was lower than that for males (Table 6). Although we failed to find a statistically significant difference, the females BV appeared to be lower than the male BV, probably owing to the higher fatty contents in the body.

Blood volume is known to vary greatly among individuals. However, the coefficient of variance of the BV was 17%–19%, which was quite a bit lower than that of the cardiac index (35.7%). Thus, the distribution of BV in our study was not wider than that of the other param-

eters. He et al. reported the accuracy of this PDD and confirmed good repeatability as well [15]. Therefore, we believe that the standard value for BV and its distribution is close to the distribution of the real population.

During the 1960s, blood volume was measured perioperatively using radioisotope. Since preload parameters have come into clinical use, such quantitative analysis of BV has been replaced. Herewith we propose a standard value of BV for clinical studies because we expect that measuring BV may offer a better parameter for specific occasions than the preload parameters. We hope that clinical trials to examine the significance of this parameter may thereby become more feasible.

Putative role of BV value for hemodynamic management

This study was aimed at determining a standard BV value as a reference for future clinical studies that could potentially examine the role of the BV value in hemodynamic management. After we gathered data from several institutions, we investigated whether there were any statistical findings with respect to the BV value and hemodynamics. Incidentally, we statistically demonstrated that hypovolemia contributed to a reduction in BP after induction of anesthesia; this result appears to be physiologically reasonable, as it agrees with longstanding tenets.

The 95% confidence interval for the odds ratio of BV for reduced BP was large (crossing 1.0). This large range can be attributed to the fact that our entire patient sample underwent elective surgery (i.e., a population that rarely has low BV). This study design was not primarily intended for the assessment of hemodynamically compromised patients. Had we included emergency cases in this study, the odds ratio presumably would have remained within a narrow range of more than 1.0. However, it is currently ethically impossible to induce uniform anesthesia in such a patient group.

Adverse reaction of ICG

Indocyanine green is widely used in hepatic function tests and for retinal imaging. Because ICG contains iodide, an allergic reaction is possible, although we did not experience any allergic reactions in this series of studies. Hope-Ross et al. reported in their retinal imaging study of 1923 that only eight patients had shown reactions to ICG and concluded that ICG is much safer than fluorescein [16]. Most of their cases appeared to be pseudo-allergic reactions. ICG was used at most 1–5 $mg \cdot kg^{-1}$, which was much higher than our dose of 20 mg (<0.5 $mg \cdot kg^{-1}$). Therefore, we were not concerned with ICG reactions using this measuring technique, although it should be noted that we should confirm in advance that the patients were not allergic to iodide.

Conclusions

We present the standard value and variation of circulating BV as measured by pulse dye-densitometry. There was no significant difference observed in the obtained value with respect to age. This value could be a reference for using bedside BV estimation during anesthesia. We also obtained the clinical significance of the BV value from a statistical analysis; the BV value was significantly linked to the reduction in BP after induction of anesthesia.

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