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EXPERIMENTAL

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# Glucose dilution can detect fluid redistribution following phentolamine infusion in dogs

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**Abstract** *Objective*: We have recently reported that the initial distribution volume of glucose (IDVG) reliably measures the central extracellular fluid (ECF) volume in the presence of fluid gain or loss. However, it is not clear if IDVG consistently reflects central-ECF volume when redistribution of fluid occurs in the absence of fluid gain or loss. This study was designed to investigate changes in fluid volumes during phentolamine infusion in dogs.
*Design*: Prospective animal study.
*Setting:* Institutional animal research laboratory.
*Subjects*: Fourteen anesthetized and ventilated mongrel dogs.
*Interventions*: Anesthetized animals were mechanically ventilated and received infusions of normal saline ($n = 7$) or phentolamine (10 μg kg min) ($n = 7$). Plasma volume was estimated using the indocyanine green (ICG) dilution method (PV-ICG) and IDVG was calculated using a one-compartment model by simultaneous administration of ICG 0.5 mg/kg and glucose 100 mg/kg before, during, and after infusion of either drug.
*Measurements and results*: PV-ICG during infusion was not different between groups. However, IDVG significantly decreased ($P < 0.05$) following phentolamine infusion when compared with normal saline infusion.
*Conclusion*: Our results suggest that IDVG rather than PV-ICG consistently measures central extracellular fluid volume, even when redistribution of fluid occurs.

**Key words** Phentolamine · Measurement techniques · Glucose · Indocyanine green · Fluid redistribution

## Introduction

Routine hemodynamic variables such as arterial pressure, cardiac filling pressures, and hematocrit, do not consistently indicate blood volume adequately [1, 2], leading to inadequate pharmacological support of circulation instead of fluid administration or restriction. Consequently, reduced oxygen supply to several important organs such as kidneys and gastrointestinal tract can occur from reduced blood flow or increased interstitial edema, resulting in significant increases in morbidity and mortality as well as in length of hospital stay in critically ill patients [3, 4]. Thus, evaluation of blood volume status is important for fluid management in critically ill patients. However, redistribution of blood from the central to the peripheral compartment can occur in various diseases of critically ill patients, resulting in central hypovolemia and peripheral blood pooling, even though circulating blood volume is normal. Some authorities recommend assessment of central blood volume (CBV), namely, intrathoracic blood volume, rather than total or circulating blood volume for decision making for therapeutic interventions of critically ill patients [5, 6]. Although cardiac filling pressures are routinely used as an indicator of CBV – a major determinant of cardiac preload – these pressures do not reliably indi-

cate CBV in critically ill patients [7]. Thus, an alternative simple and reliable variable is required as a measure of CBV.

Glucose does not remain in the intravascular compartment and rapidly distributes throughout the intra- and extracellular compartments when administered intravenously. Radioisotopic studies demonstrate that insulin does not affect extracellular glucose distribution kinetics or volumes [8, 9], and that size of the interstitial compartment can be derived mathematically from plasma glucose data only [10]. We have previously reported that initial distribution volume of glucose (IDVG) correlates with plasma volume estimated using the indocyanine green (ICG) dilution method (PV-ICG) [11, 12], and is essentially identical to the central extracellular fluid (ECF) volume in hypo- and hypervolemic dogs [13, 14]. Central ECF volume consists of the interstitial fluid volume of highly perfused tissues including heart, lungs, liver, brain, and kidneys in addition to plasma volume [8]. Moreover, IDVG was found to correlate with cardiac output (CO) in critically ill patients whether or not they were receiving continuous infusions of insulin and/or vasoactive drugs [15]. Although various mechanisms including cardiac preload, afterload, and myocardial contractility can affect CO, our previous study demonstrated that patients with congestive heart failure had a relatively larger IDVG than those without it [16]. These findings would allow speculation that IDVG reflects CBV, the main factor of cardiac preload, and thus indirectly affects CO. However, it is not clear whether IDVG consistently reflects the state of central-ECF volume even when redistribution of fluid occurs in the absence of fluid gain or loss. As indicated by a report where application of positive end-expiratory pressure induced a considerable decrease in CO, but did not affect PV-ICG [17], dilution volumetry cannot consistently mirror redistribution.

Phentolamine is a competitive α-adrenergic antagonist and has similar affinities for α-1 and α-2 receptors [18]. Infusion reduces splanchnic blood perfusion [19], inducing redistribution of blood, central hypovolemia, and peripheral blood pooling associated with a decrease in cardiac preload and/or afterload. Assuming that IDVG consistently measures central-ECF volume even during redistribution of blood, phentolamine infusion should produce a decrease in cardiac preload, IDVG and CO without considerable changes in PV-ICG. This study was therefore designed to investigate changes in IDVG and PV-ICG simultaneously before, during, and after phentolamine infusion in dogs and to test whether IDVG rather than PV-ICG has potential as an indicator of CBV.

## Methods

This study was approved by our institutional Animal Experiment Committee. Fourteen mongrel dogs of either sex weighing 6.5–17.5 kg were randomly allocated into the following two groups: (1) saline group: normal saline infusion; and (2) phentolamine group: phentolamine infusion 10 μg/kg/min. Following an intravenous injection of pentobarbital 30 mg/kg, all dogs were intubated and mechanically ventilated with a Servo 900C ventilator (Siemens-Elema, Stockholm, Sweden) to maintain the end-tidal carbon dioxide equivalent to approximately 40 mmHg throughout the procedure. Anesthesia was maintained with an infusion of pentobarbital 2 mg/kg/h and pancuronium bromide 0.06 mg/kg/h.

The right femoral artery was catheterized for continuous blood pressure monitoring and blood sampling. A pulmonary artery catheter (Model 93A-741H-7.5F, Baxter Healthcare, Irvine, Calif., USA) was inserted through the right femoral vein and the tip was placed in the pulmonary artery. CO was measured by a CO computer (American Edwards Laboratories, Santa Ana, Calif., USA) using 5 ml of chilled normal saline solution. An infusion of lactated Ringer's solution was continued at a rate of 4 ml/kg/h, and the urinary bladder was catheterized.

A period of 60 min was allowed for establishment of a stable circulatory state. Prior to the first glucose and ICG infusions, mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), blood temperature, and urine volume were recorded. CO was measured in duplicate and averaged randomly during the ventilation cycle. Measurements of hematocrit, total plasma protein and plasma albumin concentrations, and arterial blood gas analysis (pH, $PaO_2$, $PaCO_2$) were made. When these measurements were completed, both glucose 100 mg/kg (0.5 ml/kg) and ICG 0.5 mg/kg (0.2 ml/kg) (Daiichi Pharmacol, Tokyo, Japan) were simultaneously infused through the central venous line over 30 s. Each 2.5 ml of arterial blood sample was drawn for determination of plasma glucose and ICG concentrations, immediately before, and at 1, 2, 3, 4, 5, 7, 9, 11, 15, 20, and 30 min following glucose and ICG infusions. These data served as the pre-infusion values.

In the phentolamine group a bolus of 0.1 mg/kg i.v. was administered followed by an infusion of 10 μg/kg/min. Phentolamine was diluted with normal saline to achieve a concentration of 2.5 mg/ml. In the saline group, the same volumes of normal saline were infused. Ninety minutes after commencing phentolamine or saline infusion, the second series of measurements and blood samplings were performed as described previously [15, 16]. These data served as the during-infusion values.

Phentolamine or normal saline infusion was terminated after 120 min. Ninety minutes later, the third series of measurements and blood samplings were conducted as previously described. These data served as the post-infusion values.

Blood samples were centrifuged immediately and plasma glucose concentrations were determined using the glucose oxidase method (GA-1150 Glucose Auto and Stat, Kyoto Daiichi Kagaku, Tokyo, Japan). Plasma ICG concentrations were determined according to a spectrophotometric technique (U3200 Spectro-photometer, Hitachi, Tokyo, Japan). IDVG and the PV-ICG were calculated from plasma decay curves using a one-compartment model (OCM) with incremental values above pre-infusion from 3 to 7 min post-infusion for the former and 3 to 11 min for the latter, as described in previous reports [11, 12, 13, 14, 15, 16, 20, 21, 22, 23, 24, 25].

In a OCM, the volume of distribution (Vd) is calculated as follows:

$$Vd = Dose/Co$$

**Table 1** Cardiovascular variables. Values are presented as median (range). *PAWP*: pulmonary artery wedge pressure, *CVP*: central venous pressure, *CO*: cardiac output, *UV*: urine volume, *Pre*: before normal saline or phentolamine infusion, *During*: during normal saline or phentolamine infusion, *Post*: 90 min after discontinuation of normal saline or phentolamine infusion

| | Saline group | | | Phentolamine group | | |
|---|---|---|---|---|---|---|
| | Pre | During | Post | Pre | During | Post |
| Heart rate (bpm) | 158 (139–198) | 159 (154–183) | 153 (114–190) | 170 (126–207) | 166 (136–207) | 130 (111–183)* |
| Mean arterial pressure (mmHg) | 130 (111–164) | 145 (100–156) | 145 (130–158)* | 133 (98–159) | 123 (102–138) | 135 (81–152) |
| PAWP (mmHg) | 10 (7–14) | 13 (7–18) | 14 (7–24) | 8 (7–19) | 9 (7–13) | 10 (8–19) |
| CVP (mmHg) | 8 (6–9) | 7 (6–10) | 7 (6–10) | 6 (4–9) | 6 (3–9) | 6 (3–9) |
| CO (ml/kg/min) | 136 (106–200) | 126 (100–161) | 116 (93–178)* | 193 (117–227) | 120 (100–192)* | 100 (78–200)* |
| UV (ml/kg/h) | 0.7 (0.1–15.4) | 1.9 (0–6.3) | 1.5 (0–9.8) | 3.1 (0.1–11.7) | 2.1 (1.6–7.6) | 2.4 (0.1–2.4) |
| Body temperature (°C) | 38.2 (36.5–39.0) | 37.4 (35.1–39.0)* | 36.8 (34.3–39.9)* | 37.7 (36.8–38.8) | 36.2 (35.0–38.0)* | 34.9 (34.2–38.3)* |

* $P < 0.05$ compared with pre-infusion

where Dose = amount of drug administered, Co = initial plasma concentration at time zero after instantaneous distribution, but before the start of elimination. A two-compartment model (TCM) was also fitted to calculate the IDVG-TCM. In a TCM, the initial volume of distribution (Vd) is calculated as follows:

$$Vd = Dose/(A + B)$$

where A = intercept at time zero of the distribution phase, B = intercept at time zero of the elimination phase.

PV-ICG and IDVG were determined using a least squares regression technique to determine the line of best fit. A nonlinear multiple regression program (MULTI) was used on the NEC 9800 computer [26, 27]. Akaike's information criterion (AIC) was calculated to evaluate the exponential term of the pharmacokinetic model [28].

$$AIC = -N\ 1\ n\ (SSQ_W) + (2P)$$

where N ist the number of data points, P is the number of parameters identified in the model, and $SSQ_W$ is the weighted residual sum of squares.

A 30 s infusion of indicators instead of a bolus injection was performed in this study, as the mixed volume of the two indicators was too large to administer as a single bolus injection. The duration of the infusion affects the results of the distribution volumes, since pharmacokinetic variables of this study were derived from a formula based on a single bolus injection. The higher the rate of disappearance of the indicator from plasma, the greater the overestimation in distribution volumes as the administered indicator begins to be cleared from the plasma during infusion. According to the formula proposed by Loo and Riegelman [29], this overestimation can be corrected. Corrected volumes were used in this study.

An estimated blood volume (EBV) (ml/kg) was calculated as follows:

$$EBV = PV - ICG\ (ml/kg)/(1 - Hematocrit\ (\%)/100)$$

Numerical data are expressed as median (range). Statistical analyses were performed using the Wilcoxon signed-rank test, the Mann Whitney U-test, and regression analysis. Agreement between two compartment models, i.e., IDVG-OCM and IDVG-TCM, was examined by the statistical method described by Bland and Altman [30]. $P < 0.05$ is considered statistically significant.

## Results

Cardiovascular variables are shown in Table 1. Median MAP during phentolamine infusion was lower than the corresponding pre-infusion value; however, this failed to reach statistical significance. This tendency was not observed during saline infusion. Neither PAWP nor CVP decreased either during or after infusion in either group. CO significantly decreased during phentolamine infusion ($P < 0.05$). CO did not change during saline infusion, but there was no significant difference between groups. Post-infusion CO in both groups decreased significantly when compared with corresponding pre-infusion values ($P < 0.05$). During phentolamine infusion hematocrit was significantly lower than that during saline infusion ($P < 0.05$). Both total plasma protein and plasma albumin concentrations during and after infusion decreased when compared with the corresponding pre-infusion values ($P < 0.05$), but no differences were found between groups (Table 2).

As indicated by AIC values of PV-ICG and IDVG, convergence was consistently observed in these two volumes, even though convergence of the former was superior to the latter.

IDVG-TCM was calculated using values from 3 to 30 min on 23 occasions in a total of 42 determinations. However, in 19 determinations, administered glucose was cleared from the plasma within 15 min. A linear correlation was obtained between IDVG-OCM and IDVG-TCM ($r = 0.72$, $n = 23$, $P < 0.001$). IDVG-OCM underestimated IDVG-TCM by an average of 0.1 ml/kg and the limits of agreement ( ± 2SD) between the models were –16.7 ml/kg–16.5 ml/kg. PV-ICG-TCM could be estimated using values from 3 to 30 min on all occasions. A linear correlation was also obtained between PV-ICG-OCM and PV-ICG-TCM ($r = 0.94$, $n = 42$, $P < 0.0001$). PV-ICG-OCM overestimated PV-

**Table 2** Arterial blood gas and laboratory variables. Values are presented as median (range). *Pre*: before normal saline or phentolamine infusion, *During*: during normal saline or phentolamine infusion, *Post*: 90 min after discontinuation of normal saline or phentolamine infusion

| | Saline group | | | Phentolamine group | | |
|---|---|---|---|---|---|---|
| | Pre | During | Post | Pre | During | Post |
| pH | 7.40 (7.34–7.45) | 7.38 (7.34–7.41)* | 7.36 (7.35–7.44) | 7.38 (7.31–7.43) | 7.33 (7.29–7.43)* | 7.37 (7.32–7.42) |
| $PaCO_2$ (mmHg) | 38.2 (28.1–44.5) | 38.6 (32.7–41.9) | 38.8 (30.3–43.6) | 41.2 (35.1–45.3) | 42.3 (33.9–46.5) | 40.7 (34.6–45.4) |
| $PaO_2$ (mmHg) | 98.3 (75.8–125.8) | 120.5 (89.9–136.3)* | 108.6 (84–139.7) | 92.3 (81.9–149.4) | 110.5 (90.5–122.7) | 117.0 (89.7–143.6) |
| Base excess (mEq/l) | –0.7 (–3.2 to 0.6) | –2.9 (–4.9 to 0.9)* | –2.6 (–3.4 to 0.6)* | –0.3 (–4 to 2.4) | –3.2 (–4.5 to 0.8)* | –2.7 (–4.2 to 0.6)* |
| Hematocrit (%) | 38.2 (28.3–45.3) | 40.0 (28.7–47.6) | 39.9 (29.2–45.5) | 38.8 (33.9–43.8)# | 36.3 (28.2–43.1)# | 363 (33.0–42.8)# |
| Total plasma protein (g/100 ml) | 4.6 (4.4–6.0) | 4.3 (4.0–5.9)* | 4.4 (3.6–5.4)* | 4.8 (4.0–5.4) | 4.5 (3.4–4.8)* | 4.4 (3.2–4.6)* |
| Plasma albumin (g/100 ml) | 2.9 (2.7–3.3) | 2.4 (2.3–3.2)* | 2.4 (2.3–2.9)* | 2.8 (2.1–3.2) | 2.5 (2.0–2.7)* | 2.3 (1.8–2.6)* |

*$P < 0.05$ compared with pre-infusion
#$P < 0.05$ compared with saline group

ICG-TCM by an average of 0.6 ml/kg and the limits of agreement ( ± 2SD) between the two models were –2.6 ml/kg–3.8 ml/kg.

PV-ICG during phentolamine or saline infusion remained unchanged when compared with the corresponding pre-infusion values. Post-infusion PV-ICG in both groups decreased significantly when compared with corresponding pre-infusion values ($P < 0.05$), but no differences were found between groups.

IDVG significantly decreased ($P < 0.05$) during phentolamine infusion. IDVG did not change during saline infusion (Fig. 1, Table 3), and there was a significant difference between groups ($P < 0.05$).

EBV during phentolamine or saline infusion remained unchanged when compared with the corresponding pre-infusion values. Post-infusion EBV in both groups decreased significantly when compared with the corresponding pre-infusion values ($P < 0.05$), but there were no differences between groups.

PV-ICG/IDVG ratio during phentolamine infusion increased compared with either the corresponding pre-infusion ratio or saline group ($P < 0.05$). The post-infusion ratio in the phentolamine group tended towards pre-infusion ratios, but remained elevated ($P < 0.05$). The PV-ICG/IDVG ratio in the saline group remained unchanged throughout the experimental procedure.

Although pre-infusion CO varied markedly among dogs in either group, a linear correlation was found between IDVG and CO in the phentolamine group ($r = 0.49$, $n = 21$, $P < 0.025$) and using all data of both groups ($r = 0.37$, $n = 42$, $P < 0.02$). However, no correlation was found between PV-ICG and CO, CVP and CO or PAWP and CO using all data of either group or all data of both groups.

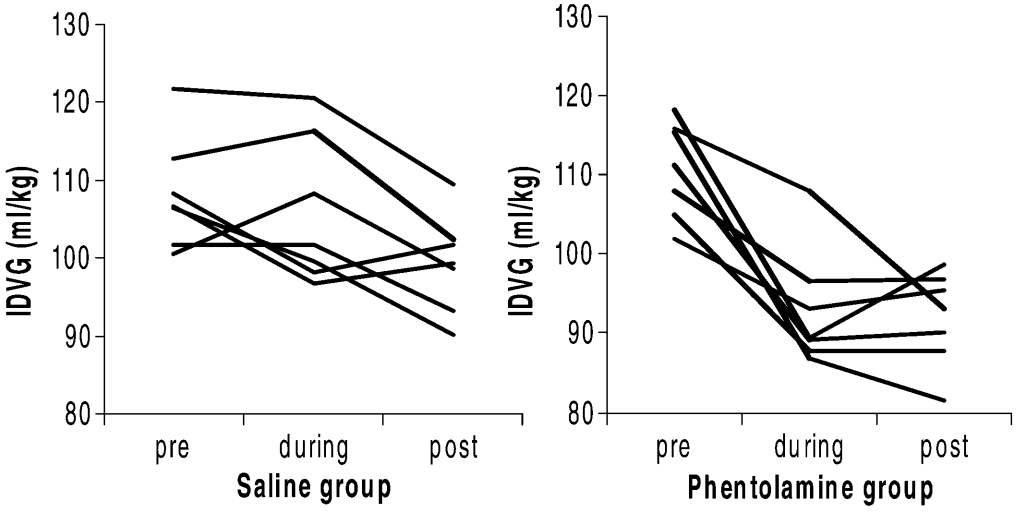


**Fig. 1** Changes in initial distribution volume of glucose (IDVG) following saline or phentolamine infusion in dogs. *Pre*: before normal saline or phentolamine infusion, *During*: during normal saline or phentolamine infusion, *Post*: 90 min after discontinuation of normal saline or phentolamine infusion

**Table 3** Pharmacokinetic variables. Values are presented as median (range). *PV-ICG*: plasma volume determined by indocyanine green, *IDVG*: initial distribution volume of glucose, *EBV*: estimated blood volume, *Pre*: before normal saline or phentolamine infusion, *During*: during normal saline or phentolamine infusion, *Post*: 90 min after discontinuation of normal saline or phentolamine infusion, *AIC*: Akaike's information criterion

| | Saline group | | | Phentolamine group | | |
|---|---|---|---|---|---|---|
| | Pre | During | Post | Pre | During | Post |
| PV-ICG (ml/kg) | 43 (35–46) | 43 (33–46) | 39 (34–43)* | 42 (36–47) | 42 (33–49) | 39 (31–48)* |
| IDVG (ml/kg) | 107 (101–122) | 102 (97–120) | 99.4 (90–109)* | 111 (102–118) | 89 (87–108)*# | 93 (82–99)*# |
| EBV (ml/kg) | 67 (61–82) | 72 (61–82) | 67 (55–75)* | 69 (65–73) | 68 (59–70) | 62 (55–73)* |
| PV-ICG/IDVG | 0.39 (0.33–0.44) | 0.39 (0.33–0.47) | 0.40 (0.35–0.42) | 0.37 (0.33–0.43) | 0.46 (0.37–0.50)*# | 0.42 (0.35–0.49)* |
| AIC for IDVG | –29.5 (–33.0 to –20.4) | –26.9 (–43.8 to –19.7) | –27.2 (–35.6 to –24.3) | –26.4 (–35.6 to –17.1) | –25.8 (–39.6 to –20.0) | –23.5 (–27.5 to –21.8)# |
| AIC for PV-ICG | –46.5 (–56.1 to –30.5) | –45.8 (–55.5 to –38.7) | –41.7 (–52.5 to –37.4) | –41.5 (–47.4 to –37.8) | –47.2 (–50.6 to –39.5) | –43.7 (–47.2 to –39.5) |

* $P < 0.05$ compared with pre-infusion
\# $P < 0.05$ compared with saline group

## Discussion

Phentolamine produces a progressive decrease in peripheral vascular resistance and is used for short-term control of hypertension in patients with pheochromocytoma [18]. In the present study, however, median arterial pressure during infusion did not differ statistically between groups. This can be partly explained as phentolamine has relatively minimal effects on supine blood pressure in normotensive subjects, even though there is a marked fall in blood pressure on standing [18]. In this study CVP and PAWP remained unchanged throughout the procedure and no correlation was found between each cardiac variable and CO. Considering these findings, a single measurement of each cardiac filling pressure was not reliable as an indicator of the state of central or intra-thoracic blood volume as reported previously [7], and these values may not detect subtle hemodynamic changes in this study.

An additional unrecognized effect of phentolamine is 5-HT receptor antagonism, and release of histamine from mast cells [18]. Histamine characteristically increases capillary permeability, probably via $H_1$ receptors. The mechanism involves endothelial cell contraction and separation at their boundaries leading to exposure of the basement membrane, which is then freely permeable to plasma proteins and water [31]. If capillary permeability increases, protein and water leakage from capillary beds would occur, resulting in an increase in hematocrit associated with a decrease in the total plasma protein concentration as described in previous reports [20, 21, 22, 23, 24]. However, this phenomenon seems unlikely as phentolamine infusion in this study did not produce any increase in hematocrit, and an infusion of lactated Ringer's solution 4 ml/kg/h throughout the procedure would not affect the stability of the interstitial matrix [32]. Additionally, either total plasma protein or plasma albumin concentrations were not significantly different between groups, even though these values decreased gradually during- and post-infusion, reflecting that the volume of blood taken from each dog totaled approximately 40 ml for each series of measurements. Thus, we believe that effects of apparent capillary protein leakage on PV-ICG determination are negligible in this study.

Both PV-ICG and EBV during phentolamine or saline infusions remained unchanged when compared with corresponding pre-infusion values in this study. In contrast, IDVG and CO during phentolamine significantly decreased compared with corresponding pre-infusion values. These findings suggest a phentolamine-induced fluid shift from the central to the peripheral compartment, and that an apparent overestimation of PV-ICG and EBV was unlikely and supports the concept that IDVG, not PV-ICG, indicates the state of central fluid volume consistently during redistribution. However, determination of PV-ICG and EBV from PV-ICG and hematocrit in this study would deserve criticism. As ICG binds mainly to albumin, PV-ICG would mirror albumin space [4]. When radioactive albumin is injected, a significant amount of albumin leaves the bloodstream during the first 10 min postinjection partly because of its relatively low molecular size (molecular weight 69,000) even in the absence of the generalized capillary protein leakage [33]. In fact, the distribution volume of $^{125}$I-albumin was 5.6 % larger than that of $^{125}$I- fibrinogen (molecular weight 330,000) [33]. Additionally, administration of crystalloid solution alone can also produce a further loss of albumin into extravascular space [34]. Considering the possible overestimation, a plasma volume marker substance having a larger molecular size – such as hydroxyethyl starch or erythrocytes volume marker substance such as sodium fluorescein [2, 4] – is required for more accurate determination of intravascular volume.

Pharmacokinetic analysis of glucose began 3 min postinfusion to ensure complete mixing with the initial distribution volume [35, 36], and data within 7 min postinfusion were fitted to a OCM. Although glucose metabolism would not appreciably modify IDVG, the greater

the interval following glucose administration, the greater the influence of basal plasma glucose levels on the pharmacokinetic behavior. This is because the size of the glucose load in this study is considerably smaller than that of a conventional intravenous glucose tolerance test. Indeed, on 19 occasions out of a total of 42 determinations in this study, glucose had been cleared from the plasma within 15 min postinfusion and therefore IDVG-TCM could not be calculated. Consequently, a OCM was applied to calculate IDVG. However, IDVG-OCM tended to underestimate the IDVG-TCM by an average of 0.1 ml/kg with the limits of agreement ( ± 2SD) between the models of –16.7 ml/kg to 16.5 ml/kg.

Although the most accurate physiological assessment of pharmacokinetic behavior of ICG is thought to be a TCM [36], the ICG dilution technique for plasma volume measurements or hepatic blood flow has been traditionally performed by fitting a monoexponential equation to plasma ICG concentration versus time data [37]. Postequilibration data within the 11 min of sampling were fitted to a OCM as in previous studies [11, 12, 13, 14, 20, 21]. In this study, a close linear correlation was obtained between PV-ICG-OCM and PV-ICG-TCM ($r = 0.94$, $n = 42$, $P < 0.0001$). PV-ICG-OCM overestimated PV-ICG-TCM by an average of 0.6 ml/kg with the limits of agreement ( ± 2SD) between the models of –2.6 ml/kg to 3.8 ml/kg. Considering this finding as well as its simple and rapid determination, we used a OCM in place of a TCM for IDVG and PV-ICG calculations in this study.

We have previously reported that IDVG correlates with CO in hypo-, normo- or hypervolemia in dogs [14, 25] and in critically ill patients [15, 16]. In this study phentolamine infusion produced a reduction of both CO and IDVG. However, different pathophysiology other than a reduction of cardiac preload or CBV may play a role in decreasing CO during phentolamine infusion. A decrease in cardiac afterload may produce a reduction of CO in the absence of a reduction of cardiac preload. Thus, IDVG should be tested to see whether this volume consistently mirrors CBV, even though the results of our previous studies allow speculation that IDVG rather than PV-ICG is an indicator of CBV or cardiac preload [23, 24]. However, CBV could not be estimated from intermittent blood sampling [38] as performed in this study. CBV is the blood volume between the pulmonary artery valve and aortic valve [5]. The mean transit time (MTT) of ICG between the pulmonary artery and aorta has been used to calculate CBV by the product of cardiac output [5]. A continuous tracing of the initial dilution curve is required to determine the MTT after bolus ICG injection [5] which was not performed in this study. ICG was infused over 30 s instead. However, CBV can also be approximated by utilizing a simultaneous ICG and glucose bolus injection, thermodilution continuous cardiac output measurement, and pulse dye densitometry (PDD) which can provide information of the MTT [38]. In our unpublished preliminary study in the consecutive 21 ICU patients, including patients with congestive heart failure, the ratio of CBV/IDVG was 0.22 ± 0.04 (SD). A linear correlation was obtained between CBV and IDVG ($r = 0.69$, $P = 0.00059$) rather than between CBV and PV-ICG ($r = 0.42$, $P = 0.055$) or between CBV and cardiac output ($r = 0.52$, $P = 0.015$). These preliminary results would support the hypothesis that IDVG is being an alternative indicator of CBV. IDVG as an indicator of CBV is a subject of a near future investigation.

As judged by pre-infusion values of heart rate, mean arterial pressure, and CO in this study, the dogs would already have increased sympatho-adrenal activity, presumably by an infusion of pancuronium bromide as well as light anesthesia with pentobarbital. These relatively high values of heart rate, mean arterial pressure, and CO were observed consistently in our previous studies [11, 12, 13, 14, 20, 21]. However, our previous experimental study suggests that this inadequately light anesthesia is unlikely as judged by relatively low catecholamine concentrations during the same pentobarbital anesthesia combined with pancuronium bromide [39]. Presumably, the individual difference in cardiac responsiveness of each dog to the anesthesia would affect these variables.

A higher PV-ICG/IDVG ratio was observed during phentolamine infusion, indicating central hypovolemia and peripheral blood pooling. We have also reported that a higher ratio was observed in burned patients [22, 23], patients with sepsis [24], experimental endotoxemia in dogs [20], and histamine-injected dogs [21]. All these reports indicated overestimation of PV-ICG as a result of general capillary protein leakage. In this study, however, overestimation induced by apparent capillary protein leakage was unlikely. Thus, a moderately high ratio alone would not consistently indicate the presence of leakage. As indicated by PV-ICG/IDVG ratio observed during phentolamine infusion in this study and the ratio during capillary protein leakage in our experimental animals [20, 21], a ratio greater than 0.50 would indicate generalized protein leakage. A ratio between 0.47 and 0.50 would indicate either possible redistribution of blood, i.e., peripheral blood pooling, or leakage. Moreover, a ratio less than 0.47 would indicate the absence of either obvious fluid shift or leakage. However, differential diagnosis of leakage and peripheral blood pooling is the subject of a future investigation in critically ill patients.

In conclusion, in the present study we have demonstrated that IDVG, not PV-ICG, mirrored peripheral blood pooling induced by phentolamine infusion. Our results suggest that IDVG rather than PV-ICG mirrors central intravascular volume, even though glucose rap-

idly distributes in the intra- and the extravascular compartments. As IDVG can be approximated by two plasma glucose samples [15, 40], IDVG is useful for the evaluation of central ECF volume.

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