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EXPERIMENTAL

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Detection of histamine-induced capillary protein leakage and hypovolaemia by determination of indocyanine green and glucose dilution method in dogs

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Abstract *Objective:* The plasma volume of histamine-induced protein capillary leakage may be overestimated when this is determined using the indocyanine green (ICG) dilution method (Vd-ICG), since this dye binds to plasma proteins. The initial distribution volume of glucose (IDVG) has been shown to indicate the central extracellular fluid volume including plasma. Accordingly, the overestimation would be detected by a higher Vd-ICG/IDVG ratio. Our study was intended to examine whether the simultaneous measurement of these two variables can evaluate histamine-induced protein leakage and associated hypovolaemia.
Design: Prospective animal study.
Setting: Institutional animal research laboratory.
Subjects: Twenty-four anaesthetized and ventilated mongrel dogs.
Interventions: Anaesthetized animals were mechanically ventilated and received infusions of normal saline ($n = 8$), histamine 50 μg/kg per h ($n = 8$), or histamine 100 μg/kg per h. The Vd-ICG and IDVG were calculated using a one-compartment model by simultaneous administration of ICG 0.5 mg/kg, and glucose 100 mg/kg followed by serial arterial blood sampling.
Measurements and results: In both histamine groups, a significant elevation of haematocrit and a decrease of plasma albumin concentration were found ($p < 0.05$). Although the IDVG decreased following histamine administration ($p < 0.05$), the Vd-ICG remained unchanged. The Vd-ICG/IDVG ratio increased in a dose-dependent manner after histamine administration ($p < 0.05$), but remained unchanged following normal saline administration.
Conclusion: The results suggest that the Vd-ICG/IDVG ratio and the IDVG are useful in evaluating the magnitude of the leakage and hypovolaemia.

Key words Histamine · Protein permeability · Measurements technique · Indocyanine green · Glucose

Introduction

Plasma histamine levels elevate appreciably in polytraumatized [1] and septic [2] patients. Thermal injury has also been reported to increase plasma histamine in rats [3]. Histamine increases capillary permeability and induces protein and water leakage, resulting in a reduction of plasma volume (PV) [4]. Evaluation of the magnitude of the capillary protein and water leakage is important in the above-mentioned critically ill patients. Although various methods for determination of capillary permeability, such as radioisotopic techniques [5, 6], capillary osmotic reflection coefficient [7] and intravital fluorescent microscopy [8], have been reported, these methods cannot be used clinically due to associated difficulties. Since the measurement of extravascu-

lar lung water (EVLW) [9] requires some surgical intervention such as the placement of relatively large catheters in both the aorta and pulmonary artery, the equipment has not become commercially available in our country because of the unfavourable risk/benefit ratio. Additionally, we recently reported that EVLW can assess the magnitude of extravascular fluid accumulation in the lung, but cannot evaluate the central-extracellular fluid (ECF) volume status [10]. Thus, there is no simple and clinically useful method for evaluating the systemic capillary permeability to either protein or water.

The distribution volume of indocyanine green (Vd-ICG) is considered equivalent to PV [11, 12]. Since ICG binds to the plasma proteins [13], the Vd-ICG can be potentially more than the PV in the presence of systemic capillary protein leakage. Assuming that the initial distribution volume of glucose (IDVG) [14] consistently indicates the ECF volume of highly perfused organs, namely the central-ECF volume including PV, the ratio of Vd-ICG/IDVG would increase in the presence of increased capillary permeability to proteins. However, it remains unclear whether the ratio indicates the magnitude of the protein leakage, and whether the IDVG itself indicates the magnitude of the associated hypovolaemia. The purpose of this study was to examine these two questions following histamine administration in dogs.

Materials and methods

The protocol was approved by our institutional Animal Experiment Committee. Twenty-four adult mongrel dogs of either sex weighing 6.0–11.0 kg were used for the experiments and divided randomly into the following three groups: 1) the control group: normal saline solution was infused, 2) the histamine 50 group: histamine was infused at a rate of 50 μg/kg per h, 3) the histamine 100 group: histamine was infused at a rate of 100 μg/kg per h. After intravenous injection of pentobarbitone 30 mg/kg, all dogs were intubated and mechanically ventilated with a Servo 900C ventilator (Siemens-Elema AB, Stockholm, Sweden) to maintain the end-tidal carbon dioxide at approximately 5 kPa throughout the procedure. Anaesthesia was maintained with an infusion of pentobarbitone 2 mg/kg per h and pancuronium bromide 0.06 mg/kg per 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 Corp., Irvine, USA) was inserted through the right femoral vein and the tip was placed in the pulmonary artery, and cardiac output (CO) was measured by CO computer (American Edwards Laboratories 9520A, Santa Ana, USA) with 5 ml of chilled normal saline solution. An infusion of lactated Ringer's solution was continued at a rate of 4 ml/kg per h. The urinary bladder was catheterized.

A period of 60 min was allowed to establish a stable circulatory state. Prior to the first glucose and ICG administration, mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and urine volume (UV) were recorded. CO was measured randomly during the ventilation cycle twice and the results averaged. Measurements of haematocrit (Hct), haemoglobin (Hb), total plasma protein (TP) and plasma albumin concentrations, and arterial blood gas analysis (pH, PaO_2, $PaCO_2$, base excess) were performed. After these measurements, both glucose 100 mg/kg (0.5 ml/kg) and ICG 0.5 mg/kg (0.2 ml/kg) (Daiichi Pharmaco Co. Ltd., Tokyo, Japan) were infused simultaneously through the central venous line over 30 s. Three millilitres of arterial blood was drawn for determining plasma glucose and ICG concentrations immediately before, and at 1, 2, 3, 4, 5, 7, 9, 11, 15, 20 and 30 min after the glucose and ICG infusions. These data served as the pre-treatment values.

Subsequently, histamine infusion was started at a rate of 50 μg/kg per h (histamine 50 group), or 100 μg/kg per h (histamine 100 group) in 8 dogs each. The histamine was diluted with normal saline to achieve concentrations of 250 μg/ml and 500 μg/ml, respectively, and infused continuously at a rate of 0.2 ml/kg per h. In the remaining 8 dogs (control group), the same amount of normal saline was infused. Ninety minutes after commencing the histamine or saline infusion, the second series of measurements and blood samplings were conducted as previously. These data served as the post-treatment values.

Blood samples were centrifuged immediately and plasma glucose concentrations were determined by using the glucose oxidase method (GA-1150 Glucose Auto and Stat, KDK Co. Ltd., Kyoto, Japan). Plasma ICG concentrations were determined according to a spectrophotometric technique (U3200 Spectro-photometer, Hitachi Co. Ltd., Tokyo, Japan). The IDVG and Vd-ICG were calculated from plasma decay curves by using a one-compartment model (OCM) with incremental values above pre-infusion from 3–7 min post-infusion for the former and 3–11 min for the latter, as described in previous reports [10, 15–24].

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

$$Vd = Dose/Co$$

where Dose = the amount of drug administered and Co = the 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 = the intercept at time zero of the distribution phase line, B = the intercept at time zero of the elimination phase.

The Vd-ICG and IDVG were determined using a least squares regression technique to find the line of best fit. A non-linear multiple regression programme (MULTI) was used on a NEC 9800 computer [25, 26]. Akaike's Information Criterion (AIC) [27] was calculated to evaluate the exponential term of the pharmacokinetic model as described in an earlier report [28].

$$AIC = -2 \log (L1) + 2np$$

where L1 = the maximum likelihood, np = the number of parameters.

Assuming that the pre-treatment Vd-ICG appropriately estimated PV, and that red blood cell volume remained unchanged during the experimental procedure despite blood sampling and potential mobilization of the red blood cells to the circulating blood from the spleen, the post-treatment PV (PV-post) (ml/kg) was also calculated from the changes of Hct (%) and the pre-treatment Vd-ICG (Vd-ICG-pre) (ml/kg) as follows:

$$PV\text{-}post = RBC\text{-}pre \times [(100 - Hct\text{-}post) / Hct\text{-}post]$$
$$RBC\text{-}pre = Vd\text{-}ICG\text{-}pre \times [Hct\text{-}pre / (100 - Hct\text{-}pre)]$$

Table 1 Changes in the cardiovascular variables (mean ± SD) (*Pre* pre-treatment values, *Post* post-treatment values, *HR* heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *MPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *UV* urine volume)

	Control group		Histamine 50 group		Histamine 100 group	
n.	8		8		8	
BW (kg)	8.6 ± 2.1		8.3 ± 1.5		8.4 ± 1.5	
	Pre	Post	Pre	Post	Pre	Post
HR (beat/min)	166 ± 23	149 ± 22	175 ± 31	170 ± 38	173 ± 23	167 ± 25
MAP (mm Hg)	140 ± 17	136 ± 15	145 ± 20	130 ± 20	133 ± 21	97 ± 19*#§
CVP (mm Hg)	9 ± 2	9 ± 1	10 ± 3	9 ± 1	9 ± 1	8 ± 2
MPAP (mm Hg)	19 ± 5	20 ± 6	18 ± 5	21 ± 8	18 ± 4	20 ± 7
PCWP (mm Hg)	13 ± 4	12 ± 4	13 ± 7	13 ± 6	12 ± 4	12 ± 6
CO (ml/kg/min)	174.6 ± 65.2	160.6 ± 56.3	179.6 ± 46.4	149.0 ± 40.8*	164.7 ± 37.4	128.2 ± 49.8*
UV (ml/kg/h)	2.0 ± 0.7	2.6 ± 1.7	2.2 ± 1.6	1.2 ± 1.3*	2.2 ± 2.5	0.2 ± 0.2*#

* $p < 0.05$ compared with the pre-treatment values
# $p < 0.05$ compared with the control group
§ $p < 0.05$ compared with the histamine 50 group

Table 2 Changes in the laboratory variables (mean ± SD) (*Pre* pre-treatment values, *Post* post-treatment values, *BE* base excess, *Hb* haemoglobin, *Hct* haematocrit, *TP* total plasma protein, *Alb* plasma albumin)

	Control group		Histamine 50 group		Histamine 100 group	
	Pre	Post	Pre	Post	Pre	Post
PH	7.355 ± 0.053	7.354 ± 0.059	7.392 ± 0.027	7.344 ± 0.077	7.375 ± 0.046	7.298 ± 0.090
$PaCO_2$ (kPa)	5.0 ± 0.7	4.9 ± 0.9	4.7 ± 0.4	4.9 ± 0.9	4.9 ± 0.6	5.3 ± 0.6
PaO_2 (kPa)	14.2 ± 2.4	14.3 ± 2.0	15.4 ± 3.3	13.8 ± 3.9	15.6 ± 2.8	13.7 ± 2.5
BE (mmol/l)	– 4.3 ± 2.4	– 4.8 ± 2.2	– 3.3 ± 2.5	– 4.8 ± 4.3	– 4.0 ± 1.8	– 6.6 ± 5.3
Hb (g/dl)	11.9 ± 1.6	11.8 ± 1.5	11.6 ± 1.6	13.1 ± 2.0*	11.9 ± 1.5	14.7 ± 2.5*#
Ht (%)	35.7 ± 4.5	35.8 ± 4.2	34.3 ± 4.9	39.1 ± 5.5*	35.3 ± 4.4	44.1 ± 8.2*#
TP (g/dl)	5.0 ± 0.9	4.8 ± 0.7	5.2 ± 0.6	4.7 ± 0.5*	5.5 ± 0.7	4.6 ± 0.7*
Alb (g/dl)	2.5 ± 0.4	2.5 ± 0.4	2.6 ± 0.4	2.3 ± 0.3*	2.6 ± 0.3	2.2 ± 0.3*

* $p < 0.05$ compared with the pre-treatment values
# $p < 0.05$ compared with the control group

where RBC-pre is the pre-treatment volume of red blood cells (ml/kg), Hct-pre is pre-treatment Hct, and Hct-post is post-treatment Hct.

The numerical data are expressed as the mean ± SD. Statistical analyses were performed using one-way analysis of variance followed by Bonferroni's multiple comparison test, paired and unpaired *t*-test, and regression analysis. A probability value of less than 0.05 was considered statistically significant.

Results

The changes in the cardiovascular variables are shown in Table 1. The values of arterial blood pH, PaO_2, $PaCO_2$ and base excess remained statistically unchanged during the experimental procedure (Table 2). Both Hb and Hct in the control group remained unchanged during the procedure, but post-treatment Hb and Hct of both histamine groups were significantly higher compared with the corresponding pre-treatment values ($p < 0.05$). The post-treatment plasma TP and albumin concentrations of both histamine groups decreased as compared with the corresponding pre-treatment values ($p < 0.05$), but no differences were found among groups (Table 2). The post-treatment Vd-ICG/IDVG ratio of the histamine 100 group increased compared with the corresponding pre-treatment ratio ($p < 0.05$). A similar pattern was also observed in the histamine 50 group, even though the difference was not statistically significant (Table 3 and Fig. 1). This ratio remained unchanged in the control group.

The mean residual plasma ICG concentration present immediately before the second administration in all the treatment groups was 0.045 ± 0.058 μg/ml, indicating that the ICG administered first had been almost cleared from the plasma at that time. Each full term of AIC was given in p2. Materials and Methods. AIC value for the plasma ICG decay curve of the three groups was less than – 40, which indicated that convergence was assumed. The mean post-treatment Vd-ICG of the control group had decreased ($p < 0.05$) compared with the corresponding pre-treatment value (Table 3). No statistically significant reduction of the Vd-ICG was observed

Table 3 Changes in the indocyanine green and glucose dilutions (mean ± SD) (*Pre* pre-treatment values, *Post* post-treatment values, *Vd-ICG* distribution volume of indocyanine green, *IDVG* initial distribution volume of glucose)

	Control group		Histamine 50 group		Histamine 100 group	
	Pre	Post	Pre	Post	Pre	Post
Vd-ICG (ml/kg)	45.9 ± 7.0	43.2 ± 5.8*	46.4 ± 7.1	44.8 ± 6.2	43.3 ± 6.3	40.6 ± 5.4
IDVG (ml/kg)	120.6 ± 19.4	118.4 ± 14.2	124.0 ± 24.4	115.4 ± 23.6*	117.0 ± 20.6	97.9 ± 17.5*
Vd-ICG/IDVG	0.38 ± 0.02	0.37 ± 0.06	0.38 ± 0.06	0.40 ± 0.06	0.37 ± 0.04	0.43 ± 0.06*

* $p < 0.05$ compared with the pre-treatment values

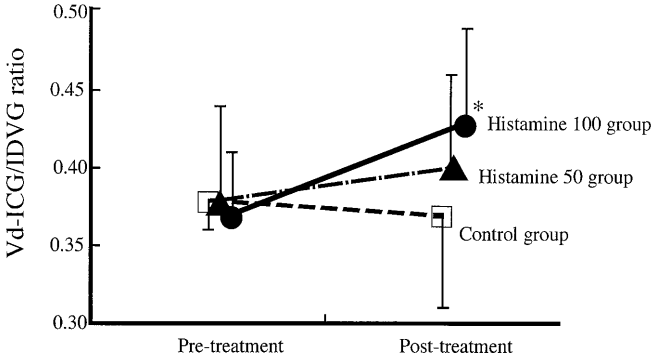

Fig. 1 Changes in the Vd-ICG/IDVG ratio (mean ± SD) (*Vd-ICG* distribution volume of indocyanine green, *IDVG* initial distribution volume of glucose)
* $p < 0.05$ compared with the pre-treatment value

following treatment in either of the histamine groups. The post-treatment PVs calculated from the pre-treatment Vd-ICG and the changes of Hct were 45.7 ± 7.6 ml/kg, 38.7 ± 7.7 ml/kg and 30.6 ± 8.2 ml/kg in the control, histamine 50 and histamine 100 groups, respectively. These post-treatment PVs calculated were less than the post-treatment Vd-ICGs in the two histamine groups ($p < 0.05$).

The mean pre-treatment plasma glucose concentration of the three groups before glucose infusion was 6.1 ± 1.2 mmol/l, and 5.8 ± 1.0 mmol/l immediately before the second administration, indicating clearance of the first infusion of glucose before the second one. The AIC values for the plasma glucose decay curves of the three treatment groups were less than – 19 indicating that convergence was assumed, since the sampling size for the IDVG was smaller than that for the Vd-ICG. No correlation was found between the IDVG and the plasma glucose concentrations present before its administration ($r = 0.27$). Although the post-treatment IDVG of the control group did not decrease significantly compared with the corresponding pre-treatment value, those of the two histamine groups decreased significantly ($p < 0.05$) (Table 3).

The IDVG-TCM was calculated using the values from 3–30 min on 32 occasions among a total of 48 determinations, excluding 16 occasions when the glucose administered had been cleared from the plasma within 15 min after infusion. A linear correlation was obtained between the IDVG-OCM and the IDVG-TCM ($r = 0.94$, $n = 32$, $p < 0.001$). The OCM overestimated the TCM by an average of 2.0 ml/kg and the limits of agreement (± 2SD) between the models were 18.0 ml/kg to – 14.0 ml/kg.

Discussion

The post-treatment Vd-ICG of the control group decreased due to the blood sampling volume of approximately 40 ml for the first series of measurements, even though a statistically significant decrease in the IDVG was not observed. The total blood volume in the control group calculated from the pre-treatment Vd-ICG and Hct was approximately 600 ml when body weight was assumed to be 8.5 kg. The total amounts of blood sampling were approximately 6–7 % of the total blood volume, resulting in a decrease in each post-treatment Vd-ICG. An infusion of lactated Ringer's solution 4 ml/kg per h as well as saline solution to flush the sampling arterial line during the procedure maintained the IDVG unchanged despite blood sampling.

In both the histamine treatment groups, significant elevation of the post-treatment Hct associated with a decrease in MAP and CO indicated a further reduction of PV. Considering the histamine-induced haemoconcentration in addition to the amount of blood sampling, a greater reduction of the post-treatment Vd-ICG would be expected in the histamine groups than in the control group. However, the post-treatment Vd-ICG of the histamine groups remained unchanged as compared with the corresponding pre-treatment values as well as the post-treatment value of the control group. Thus, the post-treatment Vd-ICG of the histamine groups did not reflect the actual PV status. These false results were supported by the fact that the post-treatment PV was calculated from the pre-treatment Vd-ICG and the changes of Hct. If further loss of red blood cells during the experimental procedure is ignored, then the post-treatment Vd-ICG overestimates PV by approximately 120 % and 140 %, in the histamine 50 and histamine 100 groups, respectively. Mobilization of red blood cells

from the spleen to circulating blood during some types of stress, such as heavy exercise, has been described [29, 30]. There is another report demonstrating that the weight of the spleen decreased after phentolamine administration [31]. The peripheral vasodilative effect of phentolamine, and possibly histamine as well, may induce the release of blood pooled in the spleen. Further studies are required to determine the contribution of splenic stored blood to the circulating volume status, even though a decrease in CO and MAP following histamine administration did not indicate any effect of the mobilization.

Kato et al. [32] reported significant ICG leakage from the pulmonary capillary bed in experimental permeability pulmonary oedema in dogs. Histamine characteristically increases the capillary permeability, probably via H_1 receptors [4], by causing the endothelial cells to contract and separate at their boundaries, thus exposing the basement membrane, which is freely permeable to plasma proteins and water. Wang et al. [33] described overestimation of PV by the ICG dilution method in experimental endotoxaemia. Endotoxin induces systemic capillary protein leakage and hypovolaemia as well [34]. Although we did not measure the activity of histamine receptors, the fact that the plasma TP and albumin concentrations, MAP and CO obviously decreased associated with an increase in Hct in both the histamine groups suggests the presence of protein leakage and PV reduction. The ICG administered would have spread throughout not only the intravascular space, but also the extravascular space, resulting in a larger Vd-ICG than actual PV. We previously reported two burn patients who temporally had unusually large Vd-ICGs, even though other clinical variables did not support the presence of hypervolaemia [15]. Since ICG is reported to bind almost totally to plasma proteins [13], and the Vd-ICG is very similar to the PV measured by the radioisotopic labelling method [11] and Evans blue dilution method [12], the dye is an ideal plasma labelling tracer. Thus, protein leakage induced binding ICG leakage and overestimation of the Vd-ICG during increased capillary permeability.

Another important cardiovascular effect of histamine via both H_1 and H_2 receptors is capillary vasodilation, which results in the trapping of a large amount of blood in the peripheral venules [4]. A further reduction of the central-ECF volume is therefore possible due to trapping in addition to PV loss from the capillary bed. This reduction of the central-ECF volume was confirmed by a reduction of CO following histamine administration in this study. Although we reported that the IDVG reflected CO in haemorrhagic dogs [16] and in critically ill patients without heart failure [17], our other previous report demonstrated a large IDVG despite a relatively low CO in patients such as congestive heart failure [18]. Additionally, the IDVG correlates with the central-ECF volume estimated by the sucrose dilution method after haemorrhagic hypovolaemia [10, 19] and hypervolaemia [10, 20] in dogs. Presumably, the central-ECF volume status rather than CO affect the IDVG, even though IDVG is not an anatomically defined compartment and CO plays a role in determining the IDVG.

Recently, Youn et al. [28] reported that insulin does not affect the extracellular glucose distribution kinetics or volumes in conscious rats as shown by a radioisotopic study. Saccomani et al. [35] also found that the intracellular distribution volume of glucose was increased and its intracellular concentration was almost halved by hyperinsulinaemia, even though its extracellular distribution volume was unchanged in a human radioisotopic study. In the present study, no correlation was found between the plasma glucose concentration present before its administration and the IDVG. Accordingly, the changes of IDVG would not be modified appreciably by glucose metabolism. Pharmacokinetic analysis of glucose began at 3 min post-infusion to ensure complete mixing within the initial distribution volume, and data within 7 min post-infusion were fitted to an OCM. Although glucose metabolism does not appreciably modify the IDVG, the longer the interval after glucose administration, the more basal plasma glucose levels affect its pharmacokinetic behaviour, since the size of the glucose load in this study is considerably smaller than that used in the conventional intravenous glucose tolerance test. In fact, on 16 occasions of a total of 48 determinations in this study, administered glucose had been cleared from the plasma within 15 min post-infusion. When the IDVG calculated with OCM was compared with a IDVG-TCM calculated using values from 3 to 30 min on the remaining 32 occasions, it tended to overestimate the IDVG-TCM by an average of only 2.0 ml/kg. Considering the above-mentioned findings as well as simple and rapid determination, we used a OCM instead of a TCM for IDVG calculations in this study.

Glucose and ICG were infused over 30 s instead of a single bolus injection. Since pharmacokinetic variables in this study were derived from the formula based on a single intravenous bolus injection, the duration of the infusion may alter the results of the distribution volumes. However, using a mathematical equation proposed by Loo and Riegelman [36], the Vd-ICG and IDVG in this study were found to overestimate the values calculated after a single bolus injection by less than 6%, as observed previously [10, 18, 20–22]. Our previous report described the changes in the Vd-ICG and the IDVG after haemorrhage in dogs [21]. When the Vd-ICG/IDVG ratio in that report was calculated, the ratio remained unchanged before and after haemorrhage of 30 ml/kg, suggesting that the simple haemorrhagic hypovolaemia without obvious capillary protein leakage does not increase the ratio. In addition, the ratio of Vd-ICG/IDVG remained unchanged before and

after a volume challenge of 30 ml/kg in dogs [22]. On the other hand, Sakai et al. [23] reported an increase in the ratio after experimental endotoxaemia in dogs. The ratio was also increased in early post-burn patients [24]. An increase of the Vd-ICG/IDVG ratio in the presence of the increased capillary permeability was consistent with these reports [23, 24].

The chronological changes of Hct, plasma TP and albumin concentrations, UV and haemodynamic variables indirectly indicate capillary protein leakage and associated hypovolaemia. However, it is difficult to evaluate these changes with a single measurement of these variables or under the influence of various pathologies as well as fluid therapy in critically ill patients. In addition, haemodynamic variables do not change consistently until the development of obvious hypovolaemia. Measurement of the ratio would provide more evidence-based fluid therapy. As observed in early post-burn patients, the protein leakage is not consistent during the first 24 h post-burn period in all patients. Colloids are given safely, even during the first 24 h post-burn, when the ratio remains small. Furthermore, determination of the Vd-ICG and the IDVG does not require technically unfamiliar instrumentation or a radioisotopic environment.

In our previous animal studies, the absolute value of the ratio of Vd-ICG/IDVG was higher than that in the present study, though the values remained unchanged during the haemorrhage procedure [21] or volume loading [22]. Various influences, such as individual variability of each mongrel dog or experimental conditions, may affect the results. However, the present study showed that the ratio increased in a dose-dependent manner after histamine administration. We reported that a Vd-ICG/IDVG ratio of more than 0.45 was observed in four of ten severely burned patients within 24 h post-burn, and not observed in anyone after 24 h post-burn [24]. Additionally, in our unpublished data, eight of the 12 septic patients had a ratio higher than 0.45 while, in contrast, the acute myocardial infarction patients without increased capillary permeability had ratios ranging from 0.30 to 0.43. Thus, the ratio would be a useful indicator of the magnitude of capillary protein leakage, possibly with one single point determination in critically ill patients.

In conclusion, the Vd-ICG/IDVG ratio increased in association with a reduction of the IDVG after histamine administration in a dose-dependent manner. The results support the assumption that the ratio and the IDVG itself would be clinically useful indicators for determining the magnitude of histamine-induced protein leakage and associated hypovolaemia.

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