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Influence of Fluid Infusion Associated with High-volume Blood Loss on Plasma Propofol Concentrations

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Background: **It is common clinical practice to use fluid infusion to manage high-volume blood loss until a blood transfusion is performed. The authors investigated the influence of fluid infusion associated with blood loss on the pseudo–steady state propofol concentration.**

Methods: **Twenty-seven swine were assigned to a lactated Ringer's solution group, a hydroxyethyl starch group, or a threefold lactated Ringer's solution group (n = 9 in each group). After 180 min of steady state infusion of propofol at a rate of 2 mg · kg^{-1} · h^{-1}, hemorrhage and infusion were induced by stepwise bleeding followed by fluid infusion every 30 min. In each of the first two steps, 400 ml blood was collected; thereafter, 200 ml was collected at each step. Just after each bleeding step, fluid infusion was rapidly performed using a volume of lactated Ringer's solution or hydroxyethyl starch equivalent to the blood withdrawn, or a threefold volume of lactated Ringer's solution. Hemodynamic parameters and the plasma propofol concentration were recorded at each step.**

Results: **Although the plasma propofol concentration in the lactated Ringer's solution group increased with hemorrhage and infusion, it decreased in both the hydroxyethyl starch and the threefold lactated Ringer's solution groups. The propofol concentration in the hydroxyethyl starch group could be expressed by the following equation: Plasma Propofol Concentration Decrease (%) = 0.80 × Hematocrit Decrease (%) (r^2 = 0.83, P < 0.0001).**

Conclusions: **When high-volume blood loss is managed by isovolemic hemodilution, the plasma propofol concentration during continuous propofol infusion decreases linearly with the hematocrit decrease.**

ANESTHESIOLOGISTS sometimes encounter unexpected high-volume blood loss associated with surgical bleeding. Although it is common clinical practice to use fluid infusion to manage such situations, the influence of fluid infusion on the concentration of intravenous anesthetics has not been fully investigated. Hypovolemia can induce changes in pharmacokinetics, including a reduction in the volume of distribution or clearance, and this can result in an increase in the anesthetic concentration.[1–6] Hence, the pseudo–steady state concentration of intravenous anesthetics might be expected to vary depending on the fluid infusion regimen.

We recently reported the influence of hemorrhage on the pseudo–steady state propofol concentration using a stepwise hemorrhagic model in swine and concluded that the plasma propofol concentration increases by less than 20% during compensated shock but increases to 3.75 times the prehemorrhagic concentrations during uncompensated shock.[7] In this previous study, we did not perform additional fluid infusion in response to blood loss, except for maintenance administration of lactated Ringer's solution (LR).

We conducted the current study to investigate the influence of fluid infusion associated with blood loss on the amplitude of the pseudo–steady state propofol concentration. To do so, we used a stepwise hemorrhage and fluid infusion model in which, in each step, we withdrew a specific volume of blood and then administered an equivalent volume of colloid or crystalloid solution or a threefold volume of the crystalloid solution to maintain the intravascular volume.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

This study was approved by the institutional ethics committee (Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan). Twenty-seven swine (mean body weight ± SD, 30.6 ± 3.4 kg; range, 26.0–38.9 kg) were used in the study. General anesthesia was administered by isoflurane inhalation (5%) in oxygen at 5 l/min using a standard animal mask. After tracheostomy, anesthesia was maintained with 2% end-tidal isoflurane and an oxygen–air mixture (fraction of inspired oxygen = 0.6) *via* mechanical ventilation. End-tidal carbon dioxide was maintained between 35 and 40 mmHg. Lead II of an electrocardiogram was monitored with subcutaneous electrodes in the legs. A peripheral venous catheter (18 gauge) was placed in the right dorsal ear vein, and an infusion of LR was given at a rate of 5 ml · kg^{-1} · h^{-1} for 180 min before propofol infusion. A pulmonary artery catheter (5 French, four lumen; Nihon Kohden, Tokyo, Japan) and a central venous catheter (16 gauge) were inserted *via* the right jugular vein, and a catheter (16 gauge) was placed in the right femoral artery. The blood temperature of the swine was maintained between 38.0° and 39.0°C using heating lamps.

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After preparation of the animals, propofol was administered with an infusion pump (TE-312; Terumo, Tokyo, Japan) *via* a central venous catheter at a rate of 2 mg · kg^{-1} · h^{-1}. At 180 min after propofol infusion, which was sufficient time to attain an essentially steady state plasma concentration of propofol, baseline measurements of heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), systemic vascular resistance (SVR), pH, hematocrit, lactate, and arterial blood gases were recorded. These parameters were recorded 30 min after every bleeding and fluid infusion step until the end of the study.

At the beginning of the study, animals were assigned to the hydroxyethyl starch group and the LR group, *i.e.*, a group in which the circulatory blood volume was maintained and a hypovolemia group, to assess differences in the changes in plasma propofol concentration. However, after a few animals were studied, it became apparent that the changes in plasma propofol concentration in the LR group were similar to those occurring during hemorrhage without fluid infusion in our previous study.[7] Hence, we added a third group, the threefold volume of LR (3LR) group (*i.e.*, 1,200 or 600 ml infusion after 400 or 200 ml hemorrhage, respectively). This group was added to assess whether the change in propofol concentration would be close to that of the hydroxyethyl starch group when the administered volume of LR was increased and to determine whether the difference between the hydroxyethyl starch and LR groups arose from the difference in the circulatory blood volume and not the difference in the fluids. Hence, swine were assigned to the LR group (n = 9), the hydroxyethyl starch group (n = 9), or the 3LR group (n = 9). After baseline measurements had been taken, hemorrhage and infusion (H&I) was induced every 30 min until death or until a total volume of 2,000 ml blood had been exchanged. In the 3LR group, stepwise H&I was performed until a total blood–fluid exchange volume of 1,400 ml was reached. In each of the first two steps, 400 ml blood was withdrawn from the femoral artery over 4 min, and then in each subsequent step, 200 ml was withdrawn over 2 min. Just after each bleeding, the infusion solution, warmed to pig blood temperature, was administered rapidly by gravity over a period of approximately 10 min for a volume of 400 ml and over 5 min for 200 ml. In the 3LR group, another two peripheral venous catheters (18 gauge) were placed in bilateral superficial abdominal veins to achieve a threefold volume of fluid infusion over approximately the same time period used for the other groups.

Cardiac output was determined with a thermodilution computer (Cardiac Output Computer, MTC6210; Nihon Kohden) using 5 ml cold 5% glucose injected into the right atrium. The CO measurements were each made four times, and the mean of the last three values was recorded. Arterial blood samples (2 ml) were taken to determine the steady state plasma concentrations of propofol 10, 30, 60, 120, and 180 min after the start of propofol infusion. Blood samples for the propofol assay were taken 30 min after each H&I step. Propofol concentrations were assayed by high-performance liquid chromatography according to the method of Plummer.[8] The lower limit of detection was 15 ng/ml, and the mean intraassay coefficient of variation was 7.3%.

The time course of the predicted plasma propofol concentration in the absence of hemorrhage during continuous propofol infusion can be calculated using a three-compartment model in swine, as follows[9]: $Cp(t) = -A \cdot e^{-p} \cdot t - B \cdot e^{-q} \cdot t - C \cdot e^{-r} \cdot t + (A + B + C)$. A, B, C, p, q, and r were fitted by least-squares regression using the data from all animals from 0 to 180 min after the start of the propofol infusion.

Statistical Analysis

Data are expressed as mean ± SD. Arterial blood gas analysis, HR, MAP, SVR, CO, mean pulmonary arterial pressure, PCWP, CVP, hematocrit, and the plasma propofol concentration for each H&I step were analyzed by a repeated-measures one-way analysis of variance. Differences in the variables between groups were also analyzed with two-factor analyses of variance with repeated measures for one factor. Differences among the three groups after 0, 400, 800, and 1,000 ml H&I were evaluated using one-way analyses of variance, and differences between the hydroxyethyl starch and 3LR groups after 1,200 and 1,400 ml H&I were evaluated using the Student *t* test. If the analysis of variance was found to be significant, the Scheffé F test was performed for multiple comparisons. *P* values less than 0.05 were considered statistically significant.

Results

In the LR group (mean body weight ± SD, 30.5 ± 3.6 kg), five animals died after 1,200 ml H&I, two died after 1,400 ml, one died after 1,600 ml, and one died after 1,800 ml. Hence, it was possible to exchange 1,175 ± 225 ml blood without causing a fatality. In the hydroxyethyl starch group (mean body weight ± SD, 30.9 ± 2.8 kg), one animal died after 1,600 ml H&I, one died after 1,800 ml, one died after 2,000 ml, and six reached 2,000 ml without fatality. In the 3LR group (mean body weight ± SD, 30.4 ± 4.1 kg), all swine reached 1,400 ml H&I. The mean volumes of infused 5% glucose for measurement of CO were 98 ± 23 ml in the LR group, 167 ± 22 ml in the hydroxyethyl starch group, and 120 ml in the 3LR group. Bradycardia accompanied by hypotension, followed by cardiac arrest, was observed in all swine that died within 30 min after their last blood exchange.

Table 1. Arterial Blood Gas Analyses and Lactate Values for Each Group at Each Hemorrhage and Infusion Step

	Total Hemorrhage and Infusion								
	0 ml	400 ml	800 ml	1,000 ml	1,200 ml	1,400 ml	1,600 ml	1,800 ml	2,000 ml
LR group, No.	9	9	9	9	4	2	1		
pH	7.50 ± 0.03	7.48 ± 0.03	7.47 ± 0.04	7.49 ± 0.03	7.50 ± 0.02	7.49 ± 0.03	7.46		
P_{CO_2}, mmHg	35.6 ± 3.9	37.2 ± 3.2	37.7 ± 2.2	31.8 ± 5.2‖	38.6 ± 7.5	30.1 ± 6.7	28.3		
P_{O_2}, mmHg	217 ± 21.4	214 ± 28.7	221 ± 20.9	215 ± 33.3	230 ± 12.1	230 ± 3.7	246		
Base excess, mM	4.5 ± 2.3	4.6 ± 2.1	3.9 ± 1.9	0.8 ± 4.5†§	−0.8 ± 5.1	−0.5 ± 3.3	−3.5		
Lactate, mM	2.2 ± 0.8	2.4 ± 1.1	3.5 ± 2.0	5.8 ± 3.2‡‖	7.0 ± 5.6	6.3 ± 3.5	10.2		
Hydroxyethyl starch group, No.	9	9	9	9	9	9	8	7	6
pH	7.52 ± 0.03	7.51 ± 0.03	7.50 ± 0.02	7.52 ± 0.02	7.51 ± 0.03	7.51 ± 0.05	7.50 ± 0.02	7.51 ± 0.04	7.58 ± 0.13
P_{CO_2}, mmHg	35.5 ± 2.6	38.1 ± 3.0	37.9 ± 3.5	36.0 ± 1.8	35.1 ± 2.0	35.4 ± 5.1	35.5 ± 1.8	34.6 ± 2.0	38.4 ± 10.2
P_{O_2}, mmHg	208 ± 16.2	201 ± 15.1	215 ± 20.1	222 ± 23.1	213 ± 13.0	221 ± 32.3	227 ± 31.6	218 ± 21.5	228 ± 32.1
Base excess, mM	5.3 ± 1.2	4.2 ± 1.1	4.2 ± 1.0	4.2 ± 0.9	3.0 ± 1.3*	3.0 ± 0.8*	2.5 ± 2.5	2.8 ± 1.4	0.8 ± 1.6
Lactate, mM	1.9 ± 0.6	2.0 ± 0.8	2.2 ± 0.6	2.3 ± 1.1	2.5 ± 1.2	2.7 ± 1.5	3.5 ± 4.0	2.8 ± 1.3	4.0 ± 1.9
3LR group, No.	9	9	9	9	9	9			
pH	7.51 ± 0.02	7.52 ± 0.02	7.51 ± 0.02	7.50 ± 0.02	7.50 ± 0.03	7.51 ± 0.02			
P_{CO_2}, mmHg	37.2 ± 2.2	37.0 ± 2.2	36.6 ± 2.2	38.0 ± 2.3	34.9 ± 3.2	35.1 ± 3.6			
P_{O_2}, mmHg	191 ± 23.7	198 ± 17.7	205 ± 19.0	215 ± 20.5	216 ± 24.5	225 ± 24.1			
Base excess, mM	5.1 ± 1.7	5.5 ± 1.4	4.5 ± 1.3	4.8 ± 2.3	2.5 ± 3.6	2.8 ± 2.5†			
Lactate, mM	1.8 ± 0.6	2.3 ± 0.9	2.7 ± 0.9	2.9 ± 1.3	3.9 ± 2.8	3.8 ± 2.9*			

* Significant difference from the value at 0 ml. † Significant difference from the values at 0 and 400 ml. ‡ Significant difference from the values at 0, 400, and 800 ml. § Significant difference *vs.* 3LR group. ‖ Significant difference *vs.* hydroxyethyl starch and 3LR groups.

LR = lactated Ringer's solution; 3LR = threefold volume of lactated Ringer's solution; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

Table 1 shows the arterial blood gas analyses and lactate values of each group at each H&I step. Base excess decreased and lactate increased with stepwise H&I in all groups, and especially in the LR group. Rapid changes were observed, and swine developed significant lactic acidemia after the blood–fluid exchange volume exceeded 1,000 ml. The HR, MAP, SVR, and CO values during stepwise H&I are shown in figure 1. In the LR group, the HR response to H&I was biphasic, and MAP decreased because of the decrease in CO, despite the maintenance of SVR. In the hydroxyethyl starch and 3LR groups, HR was slightly increased, but a biphasic response was not observed. In contrast to the LR group, MAP was slightly decreased because SVR was decreased, despite the maintenance of CO. Figure 2 shows the changes in the mean pulmonary arterial pressure, PCWP, CVP, and hematocrit values during stepwise H&I. PCWP and CVP in the LR group significantly decreased, and PCWP in the 3LR group significantly decreased, whereas those in the hydroxyethyl starch group did not change significantly. Hematocrit decreased significantly in all groups, and the values of hematocrit in the hydroxyethyl starch group were significantly less than those in the LR group. Plasma propofol concentrations after infusion during stepwise H&I are shown in figure 3. The time course of the predicted propofol concentration calculated from all swine data collected between 0 and 180 min of propofol infusion (before H&I) is also shown in figure 3. The mean plasma propofol concentrations reached approximately 97% of the predicted steady state concentration at 180 min. Plasma propofol concentrations increased approximately 6, 9, and 39% from baseline at 400, 800, and 1,000 ml, respectively, in the LR group; decreased approximately 22, 30, 34, 42, and 47% from baseline at 400, 800, 1,000, 1,200, and 1,400 ml, respectively, in the hydroxyethyl starch group; and decreased approximately 17, 28, 32, 26, and 19% from baseline values at 400, 800, 1,000, 1,200, and 1,400 ml, respectively, in the 3LR group.

In the LR group, individual plasma propofol concentrations did not increase much until a critical H&I step was reached. Thereafter, the propofol concentration clearly increased. To reduce the variability of individual responses to H&I in the LR group, we defined two hemodynamic stages: compensatory shock at individual maximal HR and uncompensated shock at individual maximal H&I. The volume of blood exchanged at maximal HR was 940 ± 232 ml, CO decreased to 1.9 ± 0.2 l/min, and the plasma propofol concentration was 1.35 ± 0.26 μg/ml (a 14% increase from baseline). At the point of uncompensated shock, the CO decreased to 1.0 ± 0.5 l/min, and the plasma propofol concentration increased to 1.80 ± 0.29 μg/ml (a 52% increase from baseline). In both the hydroxyethyl starch and 3LR groups, it was difficult to identify the individual maximal HR. Although all animals in both groups were alive after 1,400 ml H&I, CO significantly decreased in three swine of the 3LR group; 3.3 ± 0.3, 2.8 ± 0.1, 2.2 ± 0.7, and 1.6 ± 0.4 l/min at 800, 1,000, 1,200, and 1,400 ml, respectively. In the hydroxyethyl starch group, the CO values of all swine remained normal until 1,400 ml.

Figure 4 shows the relation between the decrease in hematocrit [100 × (Hematocrit at Baseline − Hematocrit)/Hematocrit at Baseline] and the decrease in the

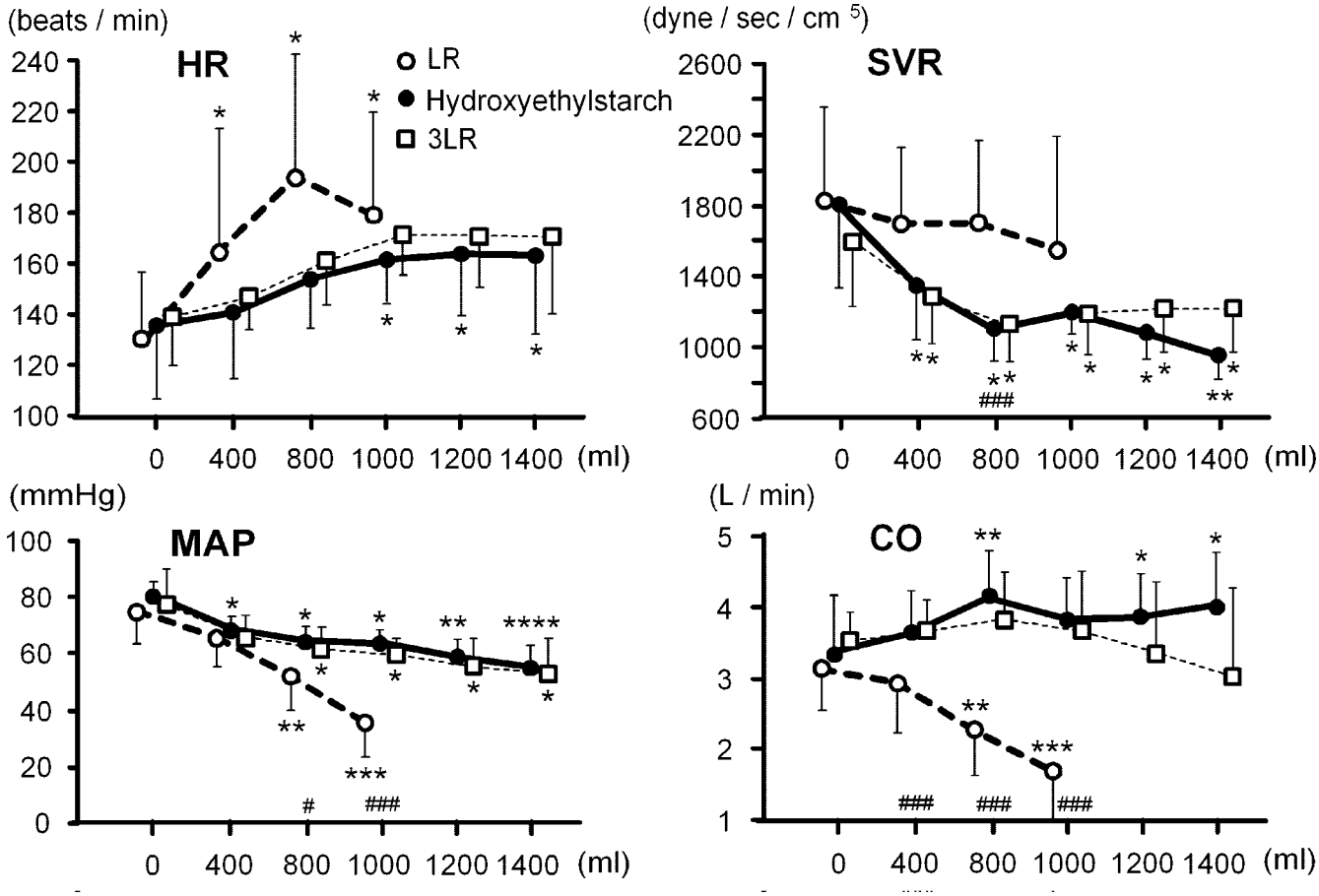

Fig. 1. Heart rate (HR), mean arterial pressure (MAP), systemic vascular resistance (SVR), and cardiac output (CO) values in the lactated Ringer's solution (LR) group, the hydroxyethyl starch group, and the threefold lactated Ringer's solution (3LR) group during stepwise hemorrhage and fluid infusion with constant propofol infusion of 2 mg · kg^{-1} · h^{-1}. * Significant difference from the value at 0 ml. ** Significant difference from the values at 0 and 400 ml. * Significant difference from the values at 0, 400, and 800 ml. **** Significant difference from the values at 0, 400, 800, and 1,000 ml. # Significant difference between the LR and hydroxyethyl starch groups. ### Significant difference between the LR and hydroxyethyl starch groups and between the LR and 3LR groups.**

plasma propofol concentration [100 × (Plasma Propofol Concentration at Baseline − Plasma Propofol Concentration)/Plasma Propofol Concentration at Baseline]. Linear regression of the raw data in each group gave the following relations: y = −0.93x, $r^2 = 0.49$ ($P = 0.0001$) for the LR group; y = 0.80x, $r^2 = 0.83$ ($P < 0.0001$) for the hydroxyethyl starch group; and y = 0.56x, $r^2 = 0.70$ ($P < 0.0001$) for the 3LR group.

Discussion

In a recent study, we examined the influence of hemorrhage on plasma propofol concentrations using a stepwise hemorrhage model in swine after 120 min steady state infusion of propofol at a rate of 2 mg · kg^{-1} · h^{-1},[7] but we did not perform fluid infusion in response to blood loss. To address this issue and assess the influence of hypovolemia on propofol pharmacokinetics, the current study was performed. The above data show that it is possible to drain 976 ± 166 ml blood before total circulatory collapse. The SVR and HR responses to hemorrhage were biphasic. The plasma propofol concentration gradually increased during compensated shock, but only by a total of less than 20%, whereas it increased to 3.75 times the prehemorrhage concentration during uncompensated shock.

Threefold or fourfold the volume of blood lost must be replaced by LR.[10] This requirement reflects the gradual decrease of CVP and PCWP during the stepwise H&I in the LR group (fig. 2), although the retention of infused Ringer's solution increases in the presence of hypovolemia.[11] The decrease in intravascular volume causes decreases in MAP and CO, indicative of the biphasic response of HR, suggesting that the hemodynamic reactions were similar to those occurring during hemorrhage without fluid infusion, as in our previous study. The changes in plasma propofol concentrations were also similar, increasing by less than 14% at individual maximal HR and increasing by 52% at individual maximal H&I volume. When using the threefold LR volume, hemodynamics remained normal, and we were unable to divide the hemodynamics into compensated and uncom-

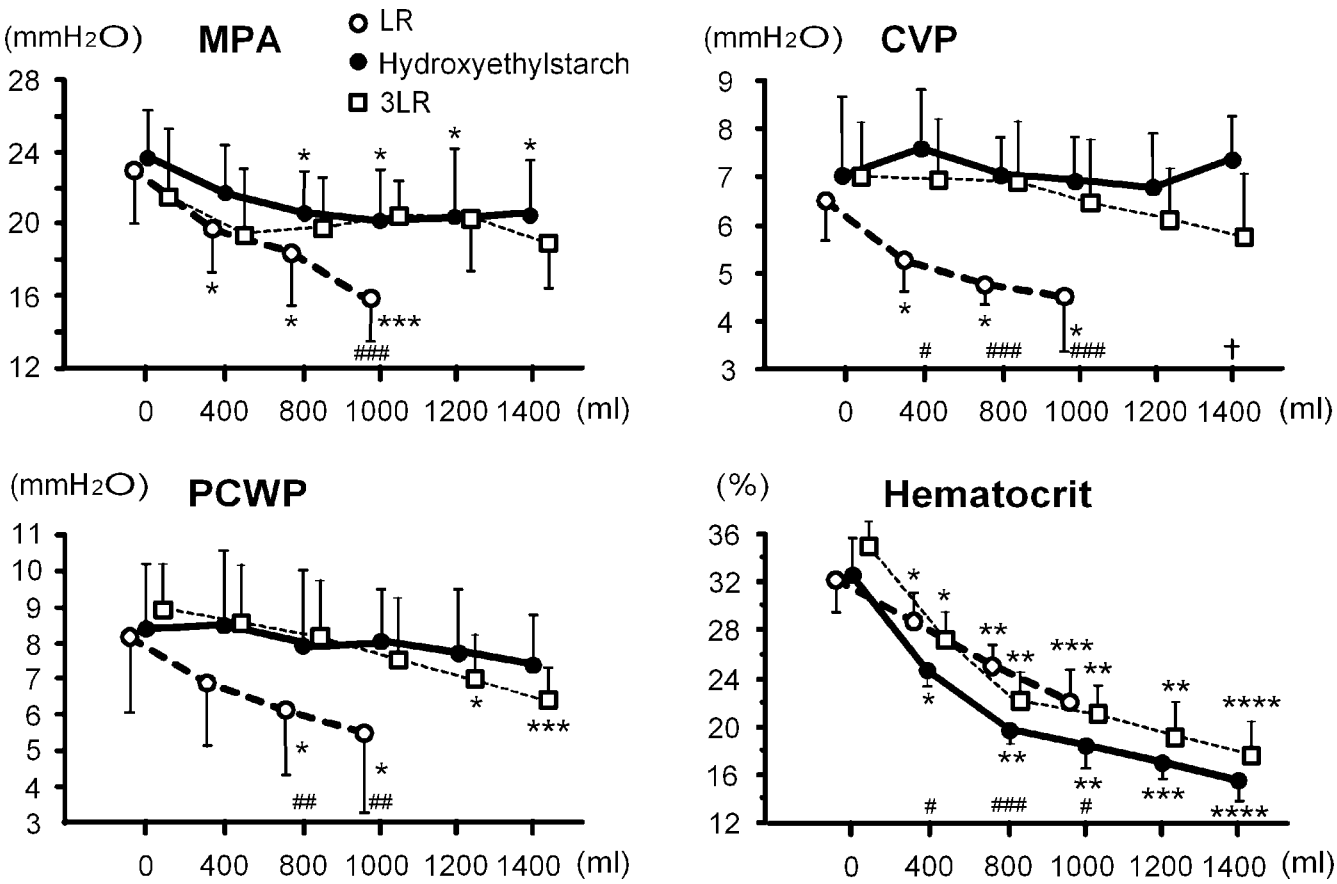

Fig. 2. Mean pulmonary arterial pressure (MPA), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and hematocrit values in the lactated Ringer's solution (LR) group, the hydroxyethyl starch group, and the threefold lactated Ringer's solution (3LR) group during stepwise hemorrhage and fluid infusion with constant propofol infusion of 2 mg · kg^{-1} · h^{-1}. * Significant difference from the value at 0 ml. ** Significant difference from the values at 0 and 400 ml. * Significant difference from the values at 0, 400, and 800 ml. **** Significant difference from the values at 0, 400, 800, and 1,000 ml. # Significant difference between the LR and hydroxyethyl starch groups. ## Significant difference between the LR and 3LR groups. ### Significant difference between the LR and hydroxyethyl starch groups and between the LR and 3LR groups. † Significant difference between the 3LR and hydroxyethyl starch groups.**

pensated shock stages in the 3LR group. PCWP significantly decreased, and CVP at 1,400 ml was significantly lower than that in the hydroxyethyl starch group (fig. 2). Because approximately 25% of LR remains in the intravascular space 50 min after administration[11,12] and, furthermore, the retention of LR slowly decreases with time, hypovolemia seemed to develop with progression of the stepwise H&I. Although the plasma propofol concentration decreased, similar to that of the hydroxyethyl starch group in the early steps of H&I (a linear regression of the data until 1,000 ml in the 3LR group yielded the equation $y = 0.78x$; $r^2 = 0.87$, $P < 0.0001$), the values at 1,200 ml and 1,400 ml seemed to stray from the line and tended to show an increase (fig. 4). In the hydroxyethyl starch group, the hemodynamic parameters, including CVP and PCWP, remained normal. The same volume of hydroxyethyl starch was able to maintain an adequate preload up to 1,400 ml H&I and achieved isovolemic hemodilution. The plasma propofol concentration decreased almost linearly in relation to the decrease in hematocrit.

To discuss the changes in the plasma propofol concentration during different stages of fluid infusion, we define the following three conditions: isovolemic hemodilution with maintenance of the circulatory blood volume, hypovolemic hemodilution with failure to maintain the circulatory blood volume (before uncompensated shock), and hypovolemic hemodilution during uncompensated shock.

Isovolemic Hemodilution with Maintenance of the Circulatory Blood Volume

In the hydroxyethyl starch group and the early steps (until 1,000 ml) of H&I in the 3LR group, the plasma propofol concentration decreased almost linearly in relation to the decrease in hematocrit. Aggressive fluid resuscitation therapy associated with high-volume blood loss caused a decrease in plasma propofol concentration, in contrast to the observation in numerous studies examining the influence of hemorrhagic shock on the disposition of intravenous anesthetics.[1–7] In a clinical situation during anesthesia, anesthesiologists manage to

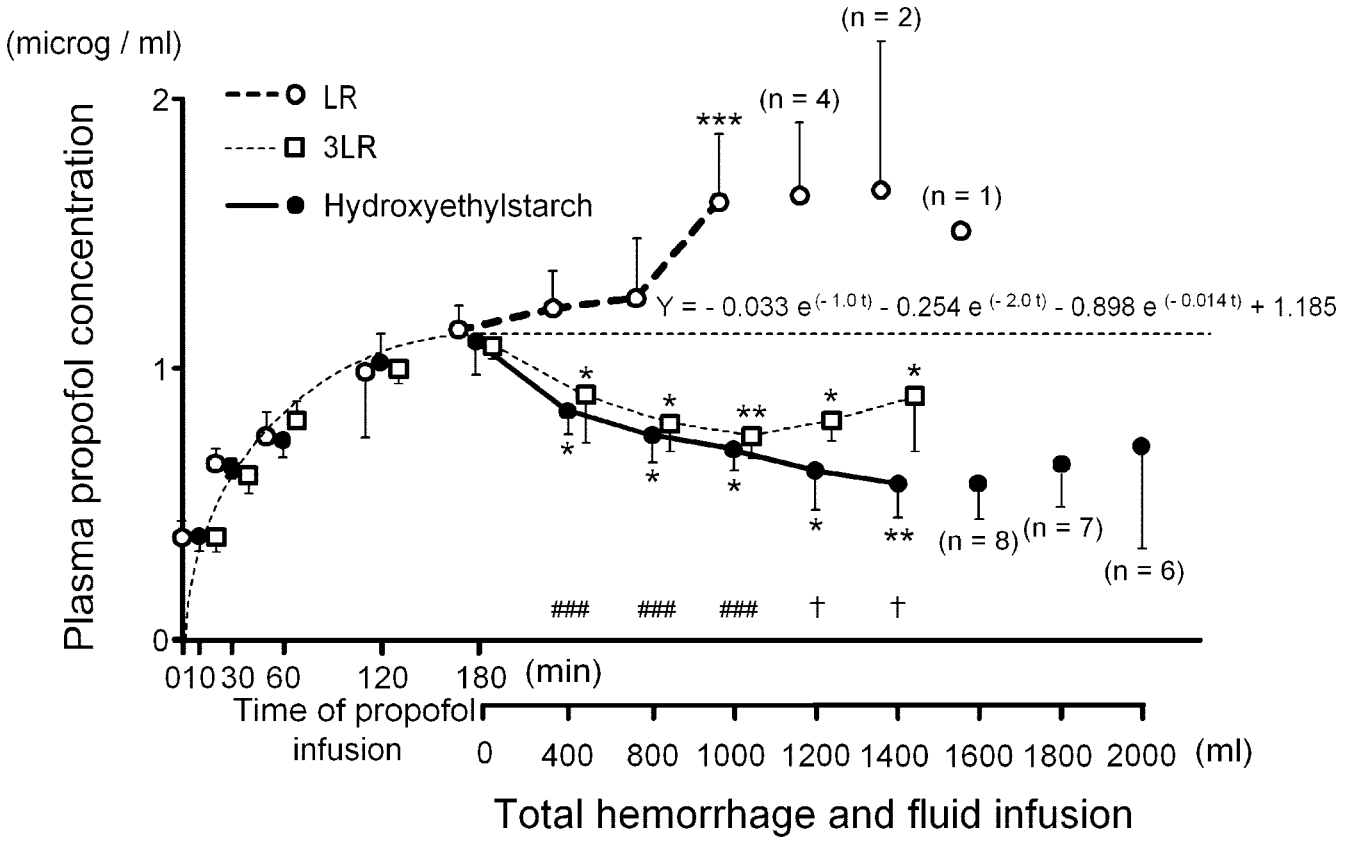

Fig. 3. Plasma propofol concentrations in the lactated Ringer's solution (LR) group, the hydroxyethyl starch group, and the threefold lactated Ringer's solution (3LR) group before and during stepwise hemorrhage and fluid infusion with constant propofol infusion of 2 mg · kg^{-1} · h^{-1}. Regression parameters were calculated by the least-squares method using individual measured propofol concentrations taken from 0 to 180 min of propofol infusion. * Significant difference from the plasma propofol concentration at 180 min (0 ml) with each group. ** Significant difference from the plasma propofol concentration at 0 and 400 ml with each group. * Significant difference from the values at 0, 400, and 800 ml. ### Significant difference between the LR and hydroxyethyl starch groups and between the LR and 3LR groups. † Significant difference between the 3LR and hydroxyethyl starch groups.**

avoid hypovolemia or hemorrhagic shock in response to high-volume blood loss using fluid infusion and blood transfusion. However, although this is the clinical situation for working anesthesiologists, the changes in plasma propofol concentration under such conditions have not been fully investigated. The plasma propofol concentration did not decrease at a 1:1 ratio with a decrease in hematocrit because propofol was administered continuously during the 30 min after each H&I step until the blood sampling time. When the circulatory blood volume and hemodynamics remained normal, the dilution effect was clearly reflected in the decrease in plasma propofol concentration.

The plasma propofol concentration shows a linear correlation with the inverse of CO in the presence of exogenous catecholamines[13,14] and when carbon dioxide tension is altered.[15] Propofol concentration was also found to correlate with the inverse of CO when the concentration was varied by hemorrhage in our previous study, but two different correlates were found. When CO is more than 2 l/min, it has little effect on the plasma propofol concentration, but when CO is less than 2 l/min, the concentration is markedly influenced by a decrease in CO.[7] In another anesthetized swine study, Van Woerkens *et al.*[16] demonstrated that isovolemic hemodilution (reduction of hematocrit from 28% to 9%) results in a doubling of the CO, primarily because of an increase in stroke volume. In the current study, CO significantly increased from 3.4 ± 0.8 l/min at baseline to 4.2 ± 0.6 l/min at 800 ml H&I (with a maximum mean value of 4.4 ± 0.6 l/min). Because the approximately 20% increase in CO might have decreased the plasma propofol concentration by approximately 10%,[14] CO might contribute at least partially to the decrease in the plasma propofol concentration.

Hypovolemic Hemodilution with Failure to Maintain the Circulatory Blood Volume (before Uncompensated Shock)

During the later steps (1,200 and 1,400 ml) of H&I in the 3LR group, the plasma propofol concentration did not decrease with H&I and no longer had a linear relation with hematocrit (fig. 4). Although CO decreased with stepwise H&I in three swine of the 3LR group, CO remained normal until 1,400 ml (averages of 4.2 ± 0.6, 4.2 ± 0.7, 4.0 ± 0.5, and 3.9 ± 0.4 l/min at 800, 1,000, 1,200, and 1,400 ml, respectively) in the other six swine.

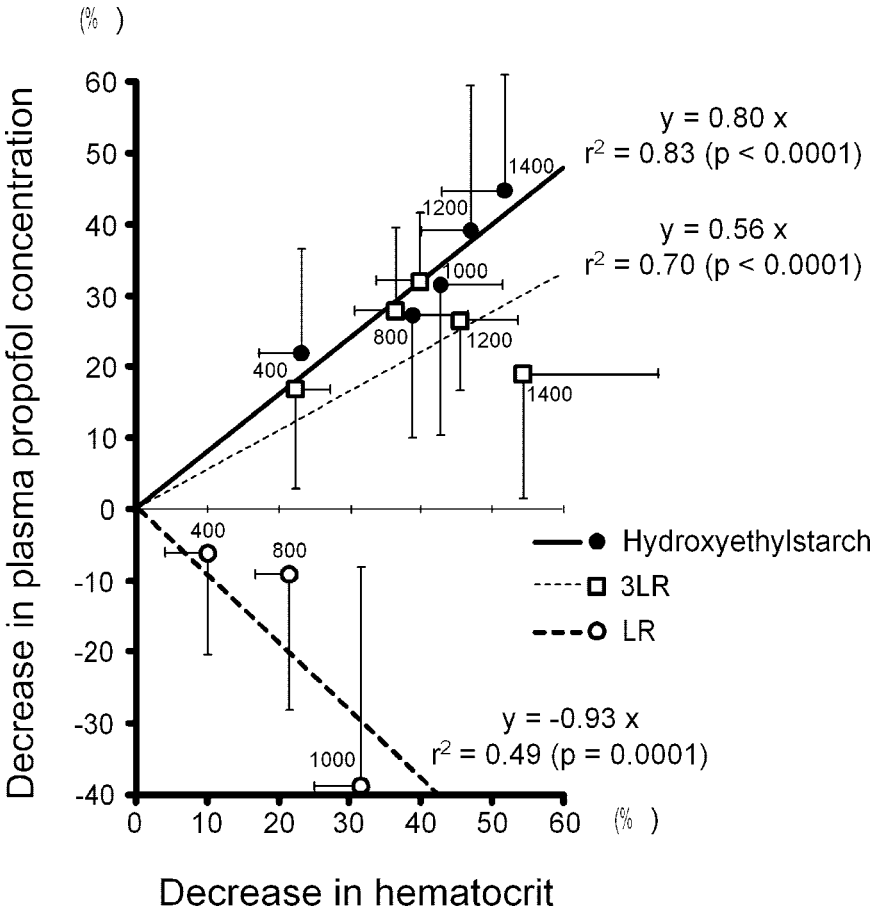

Fig. 4. Relation between the decrease in hematocrit [100 × (Hematocrit at Baseline − Hematocrit)/Hematocrit at Baseline] and the decrease in plasma propofol concentration [100 × (Plasma Propofol Concentration at Baseline − Plasma Propofol Concentration)/Plasma Propofol Concentration at Baseline] in each fluid infusion. Each point represents the mean and SD at each hemorrhage and infusion step (the numbers shown in the figure give the total blood–fluid exchange volume in each group). The linear regression analyses were based on raw data in each group (raw data are not shown). The linear regression equations are y = −0.93x, r^2 = 0.49 (P = 0.0001) in the lactated Ringer's solution (LR) group, y = 0.80x, r^2 = 0.83 (P < 0.0001) in the hydroxyethyl starch group, and y = 0.56x, r^2 = 0.70 (P < 0.0001) in the threefold lactated Ringer's solution (3LR) group.

The plasma propofol concentration in the six swine with normal CO decreased by averages of approximately 17, 27, 34, 26, and 24% from baseline values at 400, 800, 1,000, 1,200, and 1,400 ml, respectively, and similar concentration changes were observed. These results suggest that when high-volume blood loss is not adequately managed by fluid infusion and hypovolemia is induced, the plasma propofol concentration has a tendency to increase rather than decrease linearly with hematocrit, even if CO is normal. The changes in plasma propofol concentration with the same volume of LR infusion indicated that, when severe hypovolemia occurs, the dilution effect on the plasma propofol concentration is unclear. The changes in plasma propofol concentration were similar to those in our previous study during hemorrhage without fluid infusion, although the concentrations did minimally stray from their predicted values during compensated shock.

The pharmacokinetics of anesthetics in hypovolemia or hemorrhagic shock have been widely studied.[1–6,17,18] Increased effects of etomidate,[1] fentanyl,[2] propofol,[3,6] and remifentanil[5] but not γ-hydroxybutyrate[17] were reported during hypovolemia, and this is partially attributed to a decrease in clearance and in the distribution volume of anesthetics. De Paepe *et al.* have demonstrated that moderate hypovolemia in animals (induced by removing 30% of the initial blood volume) reduces distribution volume and systemic clearance of propofol[3] and, furthermore, increases end-organ sensitivity.[3,4] Johnson *et al.*[6] have demonstrated the same findings in severely hypovolemic animals (blood removal until 30 ml/kg). These findings may explain the results of the current study because even if fluid infusion is performed in response to blood loss, hypovolemia might be expected to reduce distribution volume and systemic clearance of propofol, with the result that the plasma propofol concentration seems to increase.

Hypovolemic Hemodilution during Uncompensated Shock

In the current study, we were able to divide hemodynamics between compensatory and uncompensated shock in the LR group only. A remarkable increase in the plasma propofol concentration was observed during uncompensated shock (a 52% increase from baseline). The CO decreased to 1.0 ± 0.5 l/min during uncompensated shock, and hence, the plasma propofol concentration was markedly influenced by the decrease in CO. In uncompensated shock, there is an extreme decrease in peripheral perfusion, which, when combined with decreased CO, results in very little drug distribution. Therefore, the drug being delivered tends to be retained in the

central compartment, resulting in a higher plasma propofol concentration.

Several limitations of the current study need to be addressed. Although we calculated the time course of the predicted plasma propofol concentration in the absence of H&I during continuous propofol infusion using a three-compartment model and used the predicted steady state concentration as a reference for the results in the H&I groups, interpretation of the data would be more reliable if a normovolemic control group without H&I had been included. The current study was limited because we did not measure the circulatory blood volume, and therefore, we cannot strictly assess whether isovolemia was maintained or when hypovolemia occurred during fluid infusion. In addition, isoflurane (2% end-tidal), which was used to maintain anesthesia throughout the study, might have some effect on the pharmacokinetics of propofol. Furthermore, the free propofol fraction in blood is 1.2–1.7% of the total concentration over a range of concentrations used clinically,[19] but hypoalbuminemia associated with H&I may increase the free propofol fraction. Hence, the decrease in the plasma propofol concentration associated with H&I may not necessarily lead to a decrease in the hypnotic effect of propofol.

In summary, when high-volume blood loss is managed by maintaining isovolemic hemodilution and avoiding hypovolemia, the plasma propofol concentration decreases almost linearly in relation to the decrease in hematocrit. When high-volume blood loss is not adequately managed by fluid infusion and hypovolemia is induced, the plasma propofol concentration has a tendency to increase. When hypovolemia progresses and circulation collapses, the plasma propofol concentration markedly increases, even with the effect of hemodilution. Although further investigation related to pharmacodynamic effects is necessary, the clinical implication of our study is that the pseudo–steady state concentration of propofol is influenced differently depending on the method of fluid infusion associated with high-volume blood loss.

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