

# Influence of Hemorrhage on Propofol Pseudo-Steady State Concentration

Tomiei Kazama, M.D.,\* Tadayoshi Kurita, M.D.,† Koji Morita, Ph.D.,† Jun Nakata, M.D.,‡ Shigehito Sato, M.D.§

**Background:** A small induction dose has been recommended in cases of hemorrhagic shock. However, the influence of hemorrhage on the amplitude of plasma propofol concentration has not yet been fully investigated during continuous propofol infusion. The authors hypothesized that the effect of hemorrhage on plasma propofol concentration is variously influenced by the different stages of shock.

**Methods:** After 120 min of steady state infusion of propofol at a rate of  $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , nine instrumented immature swine were studied using a stepwise increasing hemorrhagic model (200 ml of blood every 30 min until 1 h, then additional stepwise bleeding of 100 ml every 30 min thereafter, to the point of circulatory collapse). Hemodynamic parameters and plasma propofol concentration were recorded at every step.

**Results:** Before total circulatory collapse, it was possible to drain  $976 \pm 166 \text{ ml}$  (mean  $\pm$  SD) of blood. Hemorrhage of less than 600 ml (19 ml/kg) was not accompanied by a significant change in plasma propofol concentration. At individual peak systemic vascular resistance, when cardiac output and mean arterial pressure decreased by 31% and 14%, respectively, plasma propofol concentration increased by 19% of its prehemorrhagic value. At maximum heart rate, when cardiac output and mean arterial pressure decreased by 46% and 28%, respectively, plasma propofol concentration increased by 38%. In uncompensated shock, it increased to 3.75 times its prehemorrhagic value.

**Conclusions:** During continuous propofol infusion, plasma propofol concentration increased by less than 20% during compensated shock. However, it increased 3.75 times its prehemorrhagic concentration during uncompensated shock.

ANESTHESIOLOGISTS sometimes encounter unexpected high-volume blood loss associated with surgical bleeding. It is common clinical practice to reduce the induction dose of intravenous anesthetic agents in pa-

tients suffering from hemorrhagic shock to minimize any adverse hemodynamic consequences and to prevent prolonged anesthetic effects.<sup>1-6</sup> Although clinicians readily accept the notion that hemorrhagic shock alters pharmacokinetics, the influence of clinical hemorrhage on the amplitude of propofol concentration has not been fully investigated.

Hemodynamic response to hemorrhage is biphasic. During phase I (compensated shock), there is a progressive increase in central sympathetic vasoconstrictor drive and a decline in systemic vascular conductance. Consequently, arterial pressure is well maintained. Phase II (uncompensated shock) occurs abruptly. Central sympathetic vasoconstrictor drive decreases, heart rate (HR) declines, and arterial pressure collapses. The signal that triggers phase 2 remains unknown.<sup>7</sup>

To investigate the influence of various levels of blood loss on plasma propofol concentration, we examined its plasma concentration during continuous infusion by increasing hemorrhage in a stepwise manner until circulatory collapse. We hypothesized that the effect of hemorrhage on plasma propofol concentration would be influenced by the stage of shock.

## Materials and Methods

Studies of stepwise increasing hemorrhage were performed on nine commercial farm-bred young swine of both sexes (weight range, 29.2-32.7 kg; mean, 31.6 kg), since their cardiovascular response to stress is reportedly similar to that of human beings.<sup>8</sup> The study was approved by the Institutional Animal Care and Use Committee of Hamamatsu University School of Medicine. Anesthesia was induced with an intramuscular injection of 1.7 mg/kg ketamine HCl, and 2% isoflurane was inhaled through an anesthesia mask.

After tracheostomy with regional anesthesia, the animals were mechanically ventilated. Initial ventilator settings were as follows: tidal volume, 8-10 ml/kg; respiratory rate, 20 breaths/min; fraction of inspired oxygen, 40%; fraction of inspired nitrogen, 60%; no positive end-expiratory pressure. Oxygenation was monitored using a continuous pulse oximeter placed on the tongue or ear. Ventilation was monitored using an inspired-expired gas analyzer (Capnomac ULTIMA ULT-SV-31-04; Datex, Helsinki, Finland). Ventilator settings were adjusted when necessary to maintain oxygen saturation greater than 95% and arterial carbon dioxide partial pressure at 35-40 mmHg. Expired isoflurane levels were monitored and maintained at 1.8-2.0% throughout the study.

Interested readers are also directed to another article on this topic appearing in this issue. See Honan DM, Breen PJ, Boylan JF, McDonald NJ, Egan TD: Deterioration in bispectral index preceding intraoperative hemodynamic crisis: Evidence of acute alteration of propofol pharmacokinetics. ANESTHESIOLOGY 2002; 97:1303-5.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 6A.

\* Associate Professor, † Assistant Professor, ‡ Staff Anesthesiologist, § Professor and Chairman.

Received from the Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan. Submitted for publication September 28, 2001. Accepted for publication April 29, 2002. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Kazama: Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, Japan 431-31. Address electronic mail to: tkazama@hama-med.ac.jp. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

**Table 1. Lactate, Total Protein, and Hemoglobin Concentrations, Central Venous Pressure, and Arterial Blood Gas Analysis at Stepwise Acute Hemorrhage**

Hemorrhage (ml)	0	200	400	500	600	700	800	900	1,000	1,100	1,200
N	9	9	9	9	9	9	9	6	4	3	2
pH	7.45 ± 0.03	7.45 ± 0.05	7.47 ± 0.03	7.48 ± 0.02	7.46 ± 0.07	7.43 ± 0.09	7.42 ± 0.06	7.41 ± 0.05	7.41 ± 0.02	7.34 ± 0.04	7.33 ± 0
Pco <sub>2</sub> (mmHg)	37.9 ± 4.0	36.2 ± 5.6	37.0 ± 5.3	36.1 ± 4.7	33.4 ± 2.8	35.3 ± 4.8	35.1 ± 3.0	35.1 ± 3.6	34.4 ± 2.9	34.4 ± 3.6	33.3 ± 4.6
Po <sub>2</sub> (mmHg)	212 ± 15.0	233 ± 1.8	229 ± 14.5	221 ± 13.7	233 ± 22.0	234 ± 21.6	243 ± 21.1	230 ± 14.2	228 ± 14.8	220 ± 17	216 ± 23
Base excess (mm)	-0.3 ± 2.4	-0.5 ± 2.3	-0.7 ± 2.3	-1.0 ± 2.4	-1.3 ± 2.2	-1.8 ± 1.9	-2.1 ± 2.1	-2.3 ± 1.6	-3.0 ± 1.7	-4.0 ± 1.4	-5.1 ± 0.6
Lactate (mm)	1.3 ± 0.2	1.4 ± 0.3	1.8 ± 0.5	1.9 ± 0.4	2.4 ± 0.6	3.4 ± 1.2*	3.5 ± 1.6*	5.2 ± 1.7	6.5 ± 2.7	7.9 ± 0.3	8.4 ± 0.1
Total protein (g/dl)	5.4 ± 0.2	5.4 ± 0.1	5.2 ± 0.1	5.0 ± 0.0	4.8 ± 0.0	4.9 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	4.6 ± 0.2	4.5 ± 0.2	4.4 ± 0.2
Hemoglobin (mg/dl)	11.3 ± 0.9	11.4 ± 0.9	11.3 ± 1.1	11.7 ± 1.2	11.5 ± 1.1	11.4 ± 1.1	11.3 ± 1.2	10.5 ± 1.1	10.7 ± 0.9	11.3 ± 0.3	11.3 ± 0.8
CVP (mm H <sub>2</sub> O)	5.67 ± 3.2	4.8 ± 3.3	3.7 ± 3.0	3.3 ± 3.5	2.8 ± 3.1*	2.2 ± 2.9*	2.0 ± 3.3*	1.5 ± 2.0	1.5 ± 1.7	1.0 ± 1.0	0.5 ± 0.7

Values are mean ± SD.

\*Significant from hemorrhage 0 ml.

CVP = central venous pressure.

A venous catheter was inserted into an ear vein. Maintenance fluids (sodium Ringer's lactate) were infused at a rate of 5 mg · kg<sup>-1</sup> · h<sup>-1</sup>. The internal jugular vein was cannulated with a number 5 French pediatric pulmonary artery catheter for thermodilution estimates of cardiac output (CO). The femoral artery was cannulated with a 16-gauge arterial sheath to collect blood samples for analysis of propofol concentration, hemoglobin, blood gases, and lactate concentrations, and to continuously measure mean arterial pressure and HR. The arterial sheath was also used for drainage of blood.

After initial instrumentation, propofol infusion was initiated at a rate of 2 mg · kg<sup>-1</sup> · h<sup>-1</sup> through a venous line. At 120 min after propofol infusion, which was sufficient time to attain an essentially steady plasma concentration of propofol, baseline measurements of HR, mean arterial pressure, central venous pressure, CO, pH, total protein, hemoglobin, lactate, and arterial blood gases were recorded. These parameters were recorded 30 min after every stepwise bleeding until the end of the study.

Hemorrhage was induced by stepwise bleeding of 200 ml every 30 min until 1 h after baseline measurements had been taken; additional stepwise bleeding of 100 ml was performed every 30 min thereafter until circulatory collapse, which was defined as persistent low systolic arterial pressure of less than 30 mmHg. At each time point, blood was removed for over 1 min from the femoral artery. At the termination of the study, the animals were killed by propofol overdose.

Triplicate CO measurements using 5 ml saline at 0°C were completed using a CO computer (MTC6210; Nihon Koden, Tokyo, Japan). Arterial blood samples (2 ml) were taken to determine steady state plasma concentrations of propofol every 20 min after the start of propofol infusion to 120 min. Blood samples for propofol assay were taken 30 min after each instance of stepwise bleeding. Body temperature was monitored and maintained at 37–38°C throughout the study using a heating blanket and heating lamps as needed. Propofol concentrations

were assayed by high-performance liquid chromatography according to the method of Plummer.<sup>9</sup> The interassay coefficient of variation for paired samples within the concentration range of 1–6 µg/ml was between 5.1 and 9.1%, and the limit of detection was 15 ng/ml.

The time course of predicted plasma propofol concentration without hemorrhage during continuous propofol infusion can be calculated using the three-compartment model in swine as follows<sup>10,11</sup>:

$$C_p(t) = A \cdot e^{p \cdot t} + B \cdot e^{q \cdot t} + C \cdot e^{r \cdot t} - (A + B + C)$$

A, B, C, p, q, and r were fitted by least-squares regression (Microsoft Excel 8.0; Microsoft Co., Seattle, WA) using the data from 0 to 120 min after start of propofol infusion.

### Statistics

Results of hemodynamic variables, blood gas analysis, and propofol concentration were evaluated from baseline to 800 ml hemorrhage by repeated-measure analysis of variance. The analysis of variance was followed by Bonferroni-Dunn *post hoc* test and statistical significance was established at the 0.05 level.

### Results

For the nine animals studied, mean total infused fluid including the saline volume for measurement of CO was 1,041 ± 172 ml (mean ± SD) after propofol administration. Table 1 shows the lactate, total protein, and hemoglobin concentrations, as well as central venous pressure and arterial blood gas analysis during conditions of stepwise increasing hemorrhage. Animals subjected to the increasing stepwise hemorrhagic shock protocol developed a significant lactic acidemia once the shed blood volume exceeded 700 ml. Serum protein and hemoglobin concentrations did not change significantly. The body temperature of all animals remained normal during

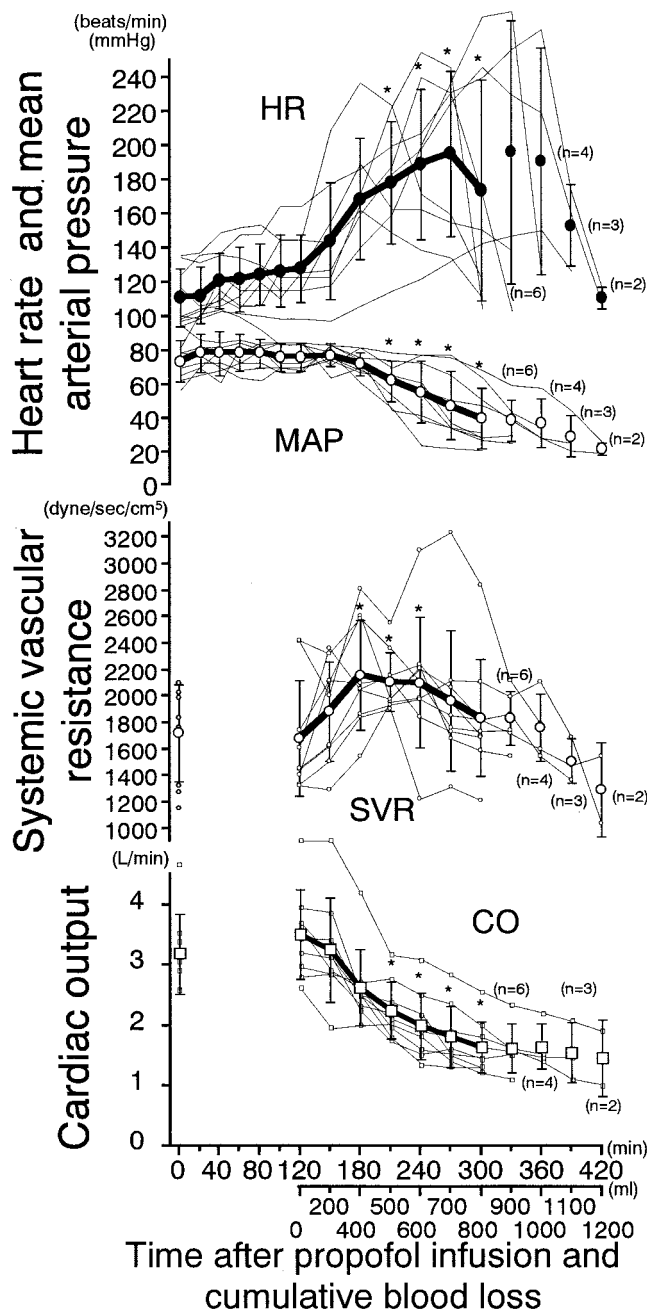


Fig. 1. Individual values and means of heart rate (HR), mean arterial pressure (MAP), systemic vascular resistance (SVR), and cardiac output (CO) before propofol infusion and during stepwise increasing hemorrhage with constant propofol infusion of  $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . \* $P < 0.05$ , significant difference from no hemorrhage (mean  $\pm$  SD).

the experimental conditions. HR, mean arterial pressure, systemic vascular resistance (SVR), and CO before propofol infusion and during stepwise increasing hemorrhage are shown in figure 1. Stepwise hemorrhage was accompanied by significant reductions in central venous pressure (table 1), mean arterial pressure, and CO (fig. 1). Before total circulatory collapse, it was possible to drain  $976 \pm 166 \text{ ml}$  of blood, *i.e.*, 51% of the estimated blood volume in each of the pigs studied. However, the

blood volumes that induced circulatory collapse varied among individual animals, ranging from 800 to 1,200 ml (fig. 1). SVR and HR responses to hemorrhage were biphasic. Individual hemodynamic responses to hemorrhage were also variable (fig. 1). Shed blood volumes that induced maximum SVR response ranged from 400 to 700 ml ( $556 \pm 113 \text{ ml}$ ), and shed blood volumes that induced maximum HR responses varied from 400 to 1,000 ml ( $688 \pm 270 \text{ ml}$ ).

Individual and mean plasma concentrations of propofol after infusion during stepwise hemorrhage are shown in figure 2. The time course of predicted propofol concentration calculated from data collected between 0 and 120 min of propofol infusion (without hemorrhage) is also shown in figure 2. The mean plasma concentration of propofol reached about 95% of predicted steady state concentration at 120 min. Individual propofol concentrations did not increase much until each critical point of hemorrhage, and thereafter increased to extremely high concentrations. The critical point varied in each animal studied. Mean propofol concentrations increased gradu-

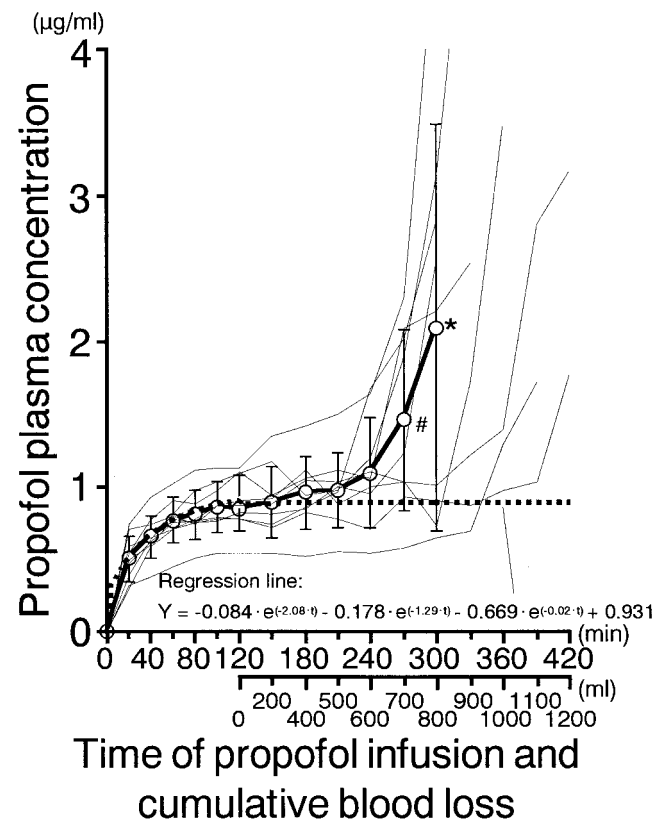


Fig. 2. Individual plasma propofol concentrations (thin lines) and mean of plasma propofol concentrations (thick line) before and during stepwise hemorrhage. The parameters of the regression line (dashed) were calculated by the least squares method using individual measured propofol concentrations taken from 0 to 120 min of propofol infusion. # $P < 0.05$ , significantly different from prehemorrhage (0 ml of hemorrhage). \* $P < 0.05$ , significantly different from 0, 200, 400, 500, 600, and 700 ml of hemorrhage (mean  $\pm$  SD).

**Table 2. Propofol Plasma Concentration, Cardiac Output, Heart Rate, Systemic Vascular Resistance, and Blood Loss at Various Shock Stages**

	Prehemorrhage	Compensatory Shock Stages		
		Stage 1 (At maximum of SVR)	Stage 2 (At maximum of HR)	Circulatory Collapse
Induced blood loss volume (ml)	0 ± 0	556 ± 113 (400–700)	688 ± 270 (400–1000)	976 ± 166 (800–1200)
SVR (dyn · s <sup>-1</sup> · cm <sup>-5</sup> )	1681 ± 435 (1324–2420)	2331 ± 414* (1905–3230)	2051 ± 297 (1543–2604)	1513 ± 260 (1038–1790)
HR (beats/min)	125 ± 27 (68–164)	194 ± 52* (92–255)	222 ± 53* (120–281)	113 ± 13 (97–138)
Cardiac output (l/min)	3.5 ± 0.7 (2.6–5.1)	2.4 ± 0.3* (1.9–2.8)	1.9 ± 0.3* (1.5–2.2)	1.4 ± 0.3* (1.00–1.90)
Lactate (mmV)	1.3 ± 0.2 (1.1–1.7)	2.4 ± 0.8 (1.2–3.8)	3.6 ± 2.5 (1.4–8.0)	5.6 ± 2.5* (2.5–8.5)
MAP (mmHg)	76 ± 8 (66–85)	65 ± 11 (46–77)	55 ± 14* (28–74)	26 ± 5* (19–34)
Propofol plasma concentration (µg/ml)	0.84 ± 0.19 (0.54–1.13)	1.00 ± 0.25 (0.54–1.50)	1.16 ± 0.27 (0.86–1.72)	3.15 ± 1.27* (1.72–5.453)

Values are mean ± SD; ranges are shown in parentheses.

\*Significant difference from prehemorrhage.

Compensatory shock: stage 1 = shock stage at individual maximum of systemic vascular resistance, stage 2 = shock stage at individual maximum of heart rate; SVR = systemic vascular resistance; HR = heart rate; MAP = mean arterial pressure.

ally, but not significantly, to 130% of prehemorrhage values at 600 ml of hemorrhage.

At 700 or 800 ml of hemorrhage, an extreme increase in propofol concentration was noted: 174% at 700 ml and 249% at 800 ml over the prehemorrhagic values. To decrease the variability of individual responses to hemorrhage, we defined hemorrhage stages as prehemorrhage, compensatory shock stage 1 (at individual maximal SVR), compensatory shock stage 2 (at individual maximal HR), and circulatory collapse (table 2). At compensatory shock stage 1, mean blood loss was 556 ml, and CO decreased from 3.5 to 2.4 l/min. However, the increase in plasma propofol concentration was small, as little as 19% of the prehemorrhagic value. At compensatory shock stage 2, CO decreased to 1.9 l/min, and plasma propofol concentration increased by 38%. At the stage of circulatory collapse, when CO decreased to 1.4 l/min, the plasma concentration of propofol increased significantly to 3.75 times its prehemorrhagic value.

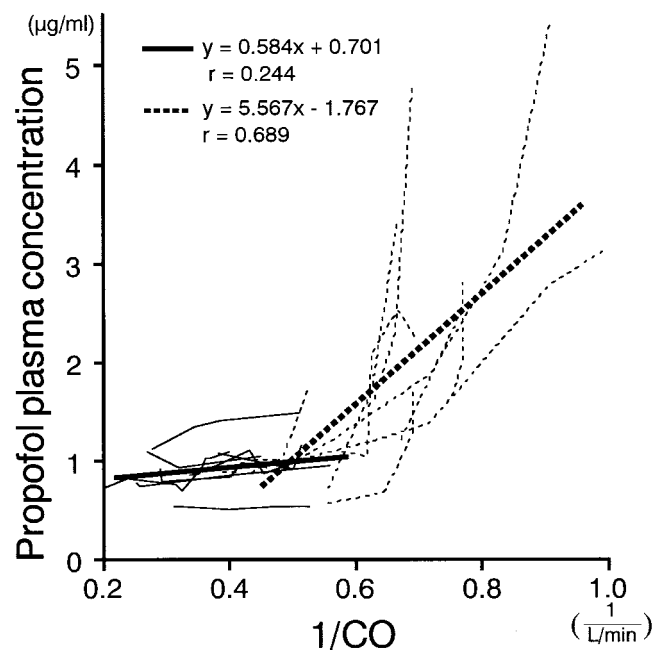
The relation between plasma propofol concentration and a reciprocal of CO was linear in each stage of shock (fig. 3). The slope that was determined from data less than individual maximum SVR was 0.584. It was much lower than the slope of 5.567 obtained from the data greater than individual maximum SVR. When CO is more than 2.0 l/min, it has little effect on propofol plasma concentration compared with more progressing shock stage.

## Discussion

In the current study, a constant propofol infusion rate (2 mg · kg<sup>-1</sup> · h<sup>-1</sup>) was maintained for 120 min before hemorrhage was initiated, and a plasma propofol concentration of 95% of the predicted steady state concentration was noted within 120 min of propofol infusion. The plasma concentration of propofol during continu-

ous infusion was thus at an essentially steady state just before hemorrhage induction.

Hemodynamic measurements and blood sampling for propofol concentrations were obtained within 30 min of each stepwise hemorrhage. Although sympathetic reflexes provide immediate compensation for blood loss, obtaining stable hemodynamic measurements and plasma propofol concentrations might take longer because the readjustment of blood volume by absorption of fluid from the interstitial spaces may take 1–48 h.<sup>12</sup>



**Fig. 3.** Individual relation between a reciprocal of cardiac output (CO) and plasma propofol concentration. The solid linear regression line was obtained by the data less than individual maximum systemic vascular resistance. The dashed linear regression line was obtained by the data beyond individual maximum systemic vascular resistance. The slope of the solid line was 0.584, which was extremely low compared with that of the broken line (5.567).

Rasmussen *et al.*<sup>13</sup> used 180 ml of stepwise bleeding every 30 min in their hemorrhagic shock study, while we used 200 or 100 ml of stepwise bleeding every 30 min until circulatory collapse. Martini *et al.*<sup>14</sup> reported that after removal of 30% of the circulating blood volume, the hemodynamic parameters at 30 min did not differ from those at 90 min after removal of blood. Although our sampling time for the plasma propofol concentration after hemorrhage may not be sufficient to attain an accurate steady state, it is sufficient to provide data pertaining to a hemodynamic pseudo steady state.

Four factors might have some involvement in the elevation of plasma propofol concentration after hemorrhage during continuous propofol infusion: CO, tissue distribution, dilution, and metabolic clearance.

#### *Cardiac Output*

Propofol concentration linearly correlates with the reciprocal of CO when it is varied by exogenous catecholamines<sup>15</sup> and when the carbon dioxide tension is altered.<sup>16</sup> In our study, too, propofol concentration correlated with the reciprocal of CO. The correlation, however, was of two different types. When hemorrhage was compensated for, the increase in propofol concentration was less than 20% of its prehemorrhagic value (table 2), and CO had only very little effect on the propofol concentration (fig. 3). When hemorrhage was uncompensated, the plasma concentration of propofol was elevated to life-threatening concentrations and was remarkably influenced by the decrease in CO (fig. 3). These findings suggest that hemorrhage influenced not only CO but also other factors to increase plasma propofol concentration.

#### *Tissue Distribution*

Induced hemorrhage decreases circulating blood volume and increases SVR in compensated shock. However, the propofol concentration was 1.00  $\mu\text{g/ml}$  even in maximum of SVR in our study (table 2), which was only a 19% increase of prehemorrhage values. In more progressing shock stages, propofol plasma concentration increased to 3.5 times of baseline value. In the final stages there is an extreme decrease in peripheral perfusion, which, when combined with decreased CO, results in very little drug distribution. The result is that the drug being delivered is almost entirely retained in the central compartment.

#### *Dilution*

In our hemorrhagic model, circulating blood may have been diluted in two ways: by intravenously infused fluid and by absorption of fluid from interstitial spaces. Our total volume of fluid infused, including the saline volume for measurement of CO, was  $1,041 \pm 172$  ml (mean), which was about  $5.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Readjustment of blood volume by absorption of fluid from the interstitial

spaces requires several hours. Taking into consideration the total effect of dilution, based on the observed decrease in total plasma protein (table 1), circulating blood was diluted by about 10% with hemorrhage of 600–900 ml.

#### *Metabolic Clearance of Propofol*

According to the sinusoidal perfusion model, the hepatic extraction of a substance is ordinarily expressed as  $1 - e^{(-k/HBF)}$ , where  $k$  is a constant for each substance.<sup>17</sup> When hepatic blood flow decreases, the dose to be extracted by the liver will correlate with the hepatic blood flow, because hepatic extraction ratio of propofol is very high at 0.87.<sup>18</sup> Hypovolemia is generally accompanied by a reduction in hepatic blood flow.<sup>19,20</sup> However, the relation between hemorrhagic shock and drug metabolism is complicated. DiPiro *et al.*<sup>21</sup> demonstrated that, although total hepatic blood flow is not appreciably affected by shock (blood loss of 50% blood volume), oxidative metabolism can be impaired. Rasmussen *et al.*<sup>13</sup> demonstrated that hemorrhage decreased total hepatic blood flow, although hepatic arterial blood flow, hepatic cell oxygenation, and metabolism were preserved prior to circulatory collapse during stepwise hemorrhage. We did not measure hepatic blood flow or hepatic metabolism of propofol in the current study. Based on these previous reports,<sup>13,21</sup> we can theorize that hepatic drug metabolism was maintained to a certain extent during compensatory shock (blood loss of 29% blood volume) despite the decrease in CO. During uncompensated shock (blood loss of 51% blood volume and greater), both hepatic blood flow and drug metabolism decreased.

Hepatic arterial flow was maintained with isoflurane,<sup>22</sup> and portal venous flow was reduced by 16% at 1.2 MAC value of isoflurane.<sup>23</sup> Isoflurane might have influenced hepatic circulation and propofol disposition in our study. However, Rasmussen *et al.*<sup>13</sup> reported that total hepatic blood flow decreased from  $152$  to  $35 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$  with a loss of 40% circulating blood volume. Isoflurane was administered at a constant concentration throughout our study. Taken together, these findings suggest that, compared with the effect of hemorrhage, isoflurane makes only minor contributions to hepatic blood.

It is a standard practice to decrease the induction dose of anesthetics in hypovolemic patients.<sup>1,3</sup> The pharmacokinetics of anesthetics in shock patients has been widely studied. Hypovolemia has been shown to reduce central compartment volume and clearance in fentanyl and propofol.<sup>4,5</sup> In addition, hemorrhage increases end-organ sensitivity to the anesthetic effect of propofol.<sup>5</sup> In case of a continuous infusion, we should decrease the propofol infusion rate in hemorrhage. However, during compensatory shock, the increase in propofol concentrations was less than 20%, and during uncompensated shock it was 275% in our study, showing that the magnitude of the decrease in infusion rate to maintain a

stable plasma concentration appears to be dependent on the stage of shock.

In conclusion, plasma propofol concentration during continuous propofol infusion increased less than 20% during compensated shock. However, it increased to 3.75 times its prehemorrhagic concentration during un-compensated shock.

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