

# Influence of Hemorrhagic Shock and Subsequent Fluid Resuscitation on the Electroencephalographic Effect of Isoflurane in a Swine Model

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**Background:** The authors have previously reported that hemorrhage does not alter the electroencephalographic effect of isoflurane under conditions of compensated hemorrhagic shock. Here, they have investigated the influence of decompensated hemorrhagic shock and subsequent fluid resuscitation on the electroencephalographic effect of isoflurane.

**Methods:** Twelve swine were anesthetized through inhalation of 2% isoflurane. The inhalational concentration was then decreased to 0.5% and maintained for 25 min, before being returned to 2% and maintained for 25 min (control period). Hemorrhagic shock was then induced by removing 28 ml/kg blood over 30 min. After a 30-min stabilization period, the inhalational concentration was varied as in the control period. Finally, fluid infusion was performed over 30 min using a volume of hydroxyethyl starch equivalent to the blood withdrawn. After a 30-min stabilization period, the inhalational concentration was again varied as in the control period. End-tidal isoflurane concentrations and spectral edge frequency were recorded throughout the study. The pharmacodynamics were characterized using a sigmoidal inhibitory maximal effect model for spectral edge frequency *versus* effect site concentration.

**Results:** Decompensated hemorrhagic shock slightly but significantly shifted the concentration–effect relation to the left, demonstrating a 1.12-fold decrease in the effect site concentration required to achieve 50% of the maximal effect in the spectral edge frequency. Fluid resuscitation reversed the onset of isoflurane, which was delayed by hemorrhage, but did not reverse the increase in end-organ sensitivity.

**Conclusions:** Although decompensated hemorrhagic shock altered the electroencephalographic effect of isoflurane regardless of fluid resuscitation, the change seemed to be minimal, in contrast to several intravenous anesthetics.

HYPOVOLEMIA increases the effect of several classes of intravenous anesthetics.<sup>1–9</sup> These findings have been explained mainly by an increase in drug concentration induced by a reduction in the distribution volume and clearance and, in some cases, by an increase in end-organ sensitivity. In a clinical situation requiring maintenance of total intravenous anesthesia, these pharmacokinetic and pharmacodynamic characteristics of intravenous anesthetics sometimes complicate the treatment of patients who have significant blood loss before or during surgery.<sup>10</sup>

Inhalational anesthetics have different pharmacoki-

netic properties. Uptake from alveoli to blood is restricted by blood solubility (blood/gas partition coefficient) and cardiac output (CO). Only a small amount of an inhalational anesthetic is metabolized, and most is eliminated through exhalation.<sup>11</sup> We have recently reported the influence of hypovolemia on the electroencephalographic effect of isoflurane using a stepwise hemorrhagic model in swine and concluded that hemorrhage, at least to a level of 30% of the initial blood volume, does not alter the electroencephalographic effect of isoflurane.<sup>12</sup> Based on these pharmacokinetic and pharmacodynamic characteristics, the use of an inhalational anesthetic, rather than an intravenous anesthetic, seems to be easier for controlling the hypnotic state for patients who have significant blood loss before or during surgery. However, our previous study was performed under conditions of compensated hemorrhagic shock, and furthermore, fluid infusion was not performed in response to blood loss, although it is common clinical practice to provide some degree of resuscitation in patients with hemorrhagic shock.

We conducted the current study to investigate the influence of more severe hypovolemia, under which a decompensated hemorrhagic shock state may be reached, and subsequent fluid resuscitation on the electroencephalographic effect of isoflurane. To do so, the changes in spectral edge frequency and end-tidal isoflurane concentration in a swine model were assessed between 0.5% and 2% inhalational concentrations in the severe hypovolemic state, which was induced by initial withdrawal of 40% of the blood volume, and after subsequent hydroxyethyl starch infusion equivalent to the blood withdrawn. We hypothesized that severe hypovolemia inducing a decompensated hemorrhagic shock state would influence the effect of isoflurane and that the alteration would not be reversed by fluid resuscitation.

## Materials and Methods

### Animal Preparation

This study was approved by the institutional ethics committee (Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan). Twelve swine (body weight range, 26.3–30.0 kg; mean  $\pm$  SD, 28.1  $\pm$  1.5 kg) were used in the study. General anesthesia was achieved by isoflurane inhalation (5%) in oxygen at 6 l/min, using a standard animal mask. After tracheostomy, anesthesia was maintained with a 2% in-

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halational concentration of isoflurane and an oxygen-air mixture (oxygen:air = 3:3 l/min) *via* mechanical ventilation. Exhalation gases were analyzed using a Capnomac Ultima (ULT-V-31-04; Datex-Ohmeda, Helsinki, Finland), and these data were recorded every 10 s throughout the study. A ventilator was set to keep end-tidal carbon dioxide between 35 and 40 mmHg during the animal preparation period, and this setting was maintained throughout the study. Lead II of an electrocardiogram was monitored with three cutaneous electrodes. 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. After these preparation steps, electroencephalographic monitoring was started by preparing the skin over the fronto-occipital regions bilaterally and placing four cutaneous electrodes (Zipprep; Aspect Medical Systems, Natick, MA). Four channels of the electroencephalogram were amplified and digitally recorded using an Aspect A-1000® electroencephalogram instrument, with software version 3.0 (Aspect Medical Systems, Natick, MA). The low-pass and high-pass filters were set at 2 and 70 Hz, respectively. Digitized raw electroencephalographic waveform data and processed electroencephalographic values were collected electronically at intervals of 5 s.

#### Experimental Protocol

After completion of the animal preparation, 500 ml lactated Ringer's solution was given *via* the central venous catheter over 30 min, and no further maintenance fluids were infused throughout the study. Baseline measurements were taken after a further 30 min, and then the inhalational isoflurane concentration was decreased from 2% to 0.5% and maintained at this level for 25 min, before being returned to 2% and maintained at this level for a further 25 min (control conditions). After control measurements, hypovolemia was induced by removing 40% of the initial blood volume (the total volume was assumed to be 70 ml/kg) from the femoral artery over 30 min. After a further period of 30 min and after confirming the stability of the electroencephalogram, the inhalational isoflurane concentration was decreased from 2% to 0.5% and maintained at this level for 25 min, before being returned to 2% and maintained at this level for a further 25 min, in a similar manner to the control (40% bleeding conditions). A volume of hydroxyethyl starch equivalent to the blood withdrawn was administered *via* the central venous catheter over 30 min, and after a further 30 min, the same inhalational concentration procedure to that described above was performed (40% bleeding plus fluid infusion conditions). Hematocrit, lactate, and arterial blood gases were measured under all conditions, and heart rate, mean arterial pressure (MAP),

central venous pressure, and CO were recorded at each inhalational concentration under all conditions. CO 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.

#### Pharmacodynamic Analysis

The pharmacologic effect of isoflurane was characterized by examining the influence of isoflurane on the spectral edge frequency (SEF; the 95th percentile of the power distribution). The SEF was related to the effect site concentration ( $C_e$ ), which was derived from the classic first-order delay of the end-tidal isoflurane concentration (Etlso):  $dC_e/dt = (Etlso - C_e) k_{e0}$ , in which  $k_{e0}$  is the elimination constant from the effect site and determines the equilibration between Etlso and  $C_e$ . The  $k_{e0}$  value was calculated for each animal using a nonlinear least squares fitting method in Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA). Optimization of  $k_{e0}$  was accomplished using the Solver tool in Excel by minimizing the area bounded by the hysteresis loop plotted between the SEF values every 10 s and the Etlso values at the respective times. Because plots of the concentration-electroencephalographic effect relation were sigmoidal, an inhibitory sigmoid  $E_{max}$  equation (Hill equation)<sup>13</sup> was used to model the relation parametrically. The equation  $E = E_0 - (E_0 - E_{max}) \times [C_e^\gamma / (C_e^\gamma + EC_{50}^\gamma)]$  was used, in which  $E$  is the predicted effect,  $E_0$  is the baseline effect,  $E_{max}$  is the maximal effect,  $EC_{50}$  is the effect site concentration that produces 50% of the maximal effect, and  $\gamma$  is a measure of curve steepness, which was used to fit the equation to data for an individual animal. The parameters in the model were estimated using nonlinear least squares fitting in Excel, through optimization with the Solver tool to minimize the sum of squares between the estimated and measured SEF values. We have also reported the coefficient of determination ( $R^2$ ) as an objective function:<sup>14</sup>  $R^2 = 1 - SSE/SST$ , where SSE, the sum of squared errors, represents the sum of the squares of the differences between observed measurements for a given time and the corresponding model prediction, and SST, the total sum of squares, stands for the sum of squares of the differences between each actual measurement and the average of all the measurements.

#### Statistical Analysis

Data are expressed as mean  $\pm$  SD. Hematocrit, lactate, arterial blood gas analysis, heart rate, MAP, central venous pressure, CO, and pharmacodynamic parameters for each state were analyzed by a repeated-measures one-way analysis of variance. If the analysis of variance was found to be significant, the Scheffé F test was per-

**Table 1. Metabolic Parameters in Each State**

	Control	40% Bleeding	40% Bleeding + Fluid Infusion
pH	7.50 ± 0.03	7.47 ± 0.05	7.52 ± 0.05†
P <sub>CO<sub>2</sub></sub> , mmHg	39.0 ± 1.9	37.8 ± 3.1	36.4 ± 5.8
P <sub>O<sub>2</sub></sub> , mmHg	274 ± 27.4	285 ± 21.5	266 ± 28.7
Base excess, mm	7.1 ± 1.5	4.5 ± 2.1*	6.9 ± 1.8†
Lactate, mm	1.6 ± 0.3	4.6 ± 1.8*	3.4 ± 1.5*
Hematocrit, %	31.1 ± 2.9	30.7 ± 2.2	19.3 ± 2.5‡

\* Significant difference vs. control. † Significant difference vs. 40% bleeding. ‡ Significant difference vs. control and 40% bleeding.

P<sub>CO<sub>2</sub></sub> = partial pressure of carbon dioxide; P<sub>O<sub>2</sub></sub> = partial pressure of oxygen.

formed for multiple comparisons. *P* values less than 0.05 were considered to be statistically significant.

## Results

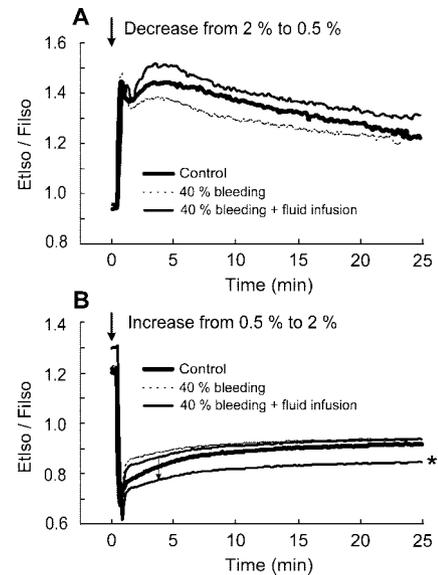
Bradycardia accompanied by hypotension followed by cardiac arrest was observed, and 2 swine died during the return phase in the 40% bleeding state. Therefore, 10 swine were used for the data analysis, and their averaged metabolic and hemodynamic parameters in each state are shown in tables 1 and 2. After removing 40% of the initial blood volume, base excess significantly decreased and lactate increased. After fluid infusion, base excess significantly reversed to the control value and lactate also showed a tendency to reverse. Hematocrit did not change after 40% bleeding but decreased after fluid infusion. Heart rate, MAP, and CO tended to increase when the inhalational concentration was decreased to

**Table 2. Hemodynamic Parameters in Each State**

	Control	40% Bleeding	40% Bleeding + Fluid Infusion
HR 2%, beats/min	109 ± 15	214 ± 29*	148 ± 19‡
HR 0.5%, beats/min	125 ± 18§	201 ± 30*	164 ± 22‡§
HR 2% <sub>2</sub> , beats/min	127 ± 23§	219 ± 20*	156 ± 20‡
MAP 2%, mmHg	74 ± 9	54 ± 9*	61 ± 10*
MAP 0.5%, mmHg	106 ± 15	69 ± 12*	101 ± 9†‡
MAP 2% <sub>2</sub> , mmHg	85 ± 10	54 ± 13*	69 ± 18‡
CVP 2%, mmHg	8.3 ± 0.9	4.0 ± 1.4*	8.1 ± 0.9†
CVP 0.5%, mmHg	7.1 ± 1.0§	4.0 ± 0.9*	6.9 ± 1.3†§
CVP 2% <sub>2</sub> , mmHg	7.8 ± 0.8	4.3 ± 1.3*	7.3 ± 1.3†§
CO 2%, l/min	3.5 ± 0.4	2.1 ± 0.4*	4.5 ± 0.9‡
CO 0.5%, l/min	4.0 ± 0.5	2.5 ± 0.4*	4.5 ± 0.7†
CO 2% <sub>2</sub> , l/min	3.5 ± 0.5	2.3 ± 0.5	3.8 ± 0.9†#

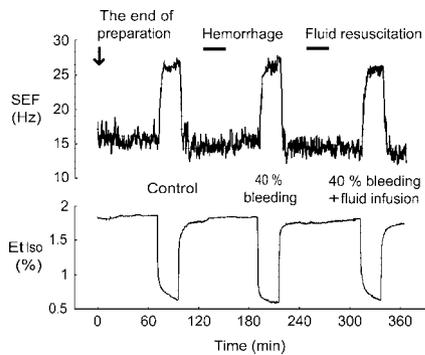
\* Significant difference vs. control. † Significant difference vs. 40% bleeding. ‡ Significant differences vs. control and 40% bleeding. § Significant difference vs. the first 2% state. || Significant differences vs. both 2% states. # Significant differences vs. the other two states.

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial blood pressure; CO 2%, CVP 2%, HR 2%, and MAP 2% = CO, CVP, HR, and MAP at the first inhalational isoflurane concentration of 2%, respectively; CO 0.5%, CVP 0.5%, HR 0.5%, and MAP 0.5% = CO, CVP, HR, and MAP at an inhalational isoflurane concentration of 0.5%, respectively; CO 2%<sub>2</sub>, CVP 2%<sub>2</sub>, HR 2%<sub>2</sub>, and MAP 2%<sub>2</sub> = CO, CVP, HR, and MAP at the second inhalational isoflurane concentration of 2%, respectively.



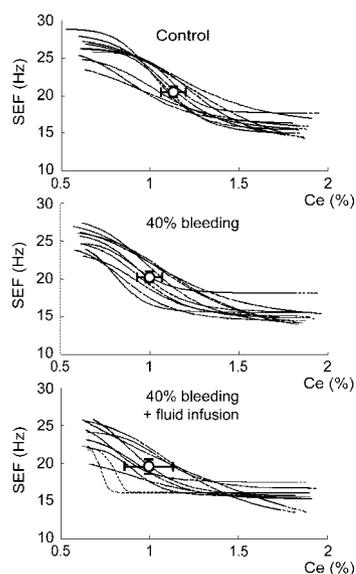
**Fig. 1.** Changes in the mean ratio of end-tidal isoflurane concentration to inspired isoflurane concentration (EtIso/Filso) during a decrease in inhalational concentration from 2% to 0.5% (A) and during an increase in inhalational concentration from 0.5% to 2% (B). \* Parallel movement of the line for 40% bleeding plus fluid infusion conditions; the line was moved to adjust the starting EtIso/Filso value.

0.5% and then decreased after the concentration returned to 2%. Hemorrhage increased heart rate and decreased MAP, central venous pressure, and CO. Figure 1 shows the changes in the mean ratio of EtIso to inspired isoflurane concentration (EtIso/Filso) during a decrease in inhalational concentration from 2% to 0.5% (fig. 1A) and during an increase in inhalational concentration from 0.5% to 2% (fig. 1B). The decrease of the EtIso/Filso ratio was rapid after hemorrhage during the concentration decrease phase and was slow after fluid infusion. The EtIso/Filso ratio increased more rapidly after hemorrhage in the return phase. The increase in the EtIso/Filso ratio observed after fluid infusion seemed to be more rapid than that in the control, but because the initial values of the EtIso/Filso ratio (or EtIso values 25 min after the inhalational concentration decreased from 2% to 0.5%) after fluid infusion were greater than those under control and 40% bleeding conditions, the increase in the EtIso/Filso ratio seemed to be slower in the control (In fig. 1, the asterisk indicates parallel movement of the line for 40% bleeding plus fluid infusion conditions; this was done to adjust the starting position.) It is probable that an increase of tissue partial pressure of isoflurane, induced by increasing tissue perfusion and blood volume, caused the slow washout after fluid infusion. Figure 2 shows the time course of both EtIso and SEF for a typical animal. Isoflurane decreased the SEF between inhalational concentrations of 0.5% and 2%, and an increase or decrease in SEF was observed shortly after a respective decrease or increase in EtIso. When the SEF values were plotted against EtIso, hysteresis was observed in all animals, as previously reported.<sup>12</sup> The hys-



**Fig. 2.** Changes in spectral edge frequency (SEF) and end-tidal isoflurane concentration (Et Iso) during an experiment in a typical animal.

teresis was collapsed by estimating the elimination constant from the effect site ( $k_{e0}$ ), resulting in the effect site concentration-SEF effect relation for isoflurane. The individual curves for all animals in each state are shown in figure 3. The correlations of the SEF to the effect site concentration were good in all states, and the correlation coefficients ( $R^2$ ) were  $0.96 \pm 0.04$  under control conditions,  $0.95 \pm 0.03$  with 40% bleeding, and  $0.90 \pm 0.08$  with 40% bleeding plus fluid infusion. The  $EC_{50}$  values (with 95% confidence intervals) were 1.12 (1.19–1.05) under control conditions, 1.00 (1.07–0.92) with 40% bleeding ( $P = 0.032$  vs. control), and 0.99 (1.13–0.85) with 40% bleeding plus fluid infusion ( $P = 0.020$  vs. control). The  $EC_{50}$  values were significantly decreased after 40% bleeding and did not reverse after fluid infusion. The SEF values (with 95% confidence intervals) at each  $EC_{50}$  were 20.5 (21.0–19.9) under control conditions, 20.2 (20.7–19.8) with 40% bleeding, and 19.3 (20.3–18.4) with 40% bleeding plus fluid infusion. The pharmacodynamic parameters are presented in table 3.



**Fig. 3.** Individual relations between the spectral edge frequency (SEF) and the effect site isoflurane concentration ( $C_e$ ) in each state. Open circles are  $EC_{50}$  values with 95% confidence intervals.

**Table 3. Pharmacodynamic Parameters**

	Control	40% Bleeding	40% Bleeding + Fluid Infusion
$k_{e0}$ , $\text{min}^{-1}$	$0.61 \pm 0.19$	$0.42 \pm 0.13^*$	$0.64 \pm 0.17^\dagger$
$E_0$ , Hz	$26.2 \pm 1.4$	$25.7 \pm 1.5$	$24.6 \pm 3.4$
$E_{\text{max}}$ , Hz	$14.8 \pm 1.5$	$14.7 \pm 1.6$	$14.1 \pm 5.0$
$\gamma$	$7.2 \pm 2.6$	$6.8 \pm 1.8$	$12.5 \pm 12.4$
$EC_{50}$ , %	$1.12 \pm 0.11$	$1.00 \pm 0.11^*$	$0.99 \pm 0.23^*$

\* Significant difference vs. control. † Significant difference vs. 40% bleeding.

$E_0$  = baseline spectral edge effect level;  $E_{\text{max}}$  = maximal spectral edge effect;  $EC_{50}$  = effect site concentration that produces 50% of the maximal spectral edge effect;  $\gamma$  = measure of curve steepness;  $k_{e0}$  = elimination constant from the effect site.

The  $k_{e0}$  decreased after 40% bleeding and reversed after fluid infusion.

## Discussion

We have investigated the influence of severe hypovolemia and subsequent fluid resuscitation on the electroencephalographic effect of isoflurane. Although alteration of the pharmacodynamics is minimal, the results of the current study indicate that hemorrhage to a level of 40% of the initial blood volume alters the electroencephalographic effect of isoflurane, in contrast to the results obtained in our previous study, in which only 30% of the initial blood volume was withdrawn.<sup>12</sup> In another study,<sup>15</sup> we observed compensatory increases of systemic vascular resistance and heart rate with increasing hemorrhage volume; the maximal systemic vascular resistance and maximal heart rate were observed at levels of 25% and 31% hemorrhage of the initial blood volume, respectively, after which increased hemorrhage volume caused progression to a decompensated state. Furthermore, hemorrhage of 40% of the initial blood volume without fluid infusion could induce circulatory collapse in some animals, and two swine died under these conditions in the current study. The hemodynamic and metabolic changes also suggested that more severe hypovolemia was induced in the current study, compared with the previous study.<sup>12</sup> The MAP and CO decreased by approximately 30–41% after 40% bleeding (compared with a decrease between approximately 16% and 27% after 30% bleeding), and lactate increased by 186% (compared with a 30% increase after 30% bleeding). Hypovolemia caused by withdrawal of 40% of the initial blood volume seemed to induce a decompensated hemorrhagic shock state. The current study indicated that when decompensated hemorrhagic shock is induced by high-volume blood loss, hemorrhage slightly alters the electroencephalographic effect of isoflurane, and subsequent fluid resuscitation does not reverse the increase in end-organ sensitivity.

The influence of blood loss on the pharmacologic properties of several intravenous anesthetics has been

discussed in many previous reports,<sup>1-9</sup> and it has been demonstrated that blood loss results in a decrease in central compartment volume, central compartment clearance, or both. These pharmacokinetic changes account for the often large differences observed in blood concentrations after equivalent dosing in hemorrhaged and control animals. Johnson *et al.*<sup>6</sup> demonstrated that hemorrhagic shock shifts the concentration-effect relation to the left, in a study investigating the influence of severe hemorrhage (30 ml/kg) on the pharmacokinetics and pharmacodynamics of propofol, in which a 2.7-fold decrease in the effect site concentration was required to achieve 50% of the maximal effect in the electroencephalogram. In their subsequent studies investigating the influence of fluid resuscitation after hemorrhagic shock on the pharmacokinetics and pharmacodynamics of propofol, Johnson *et al.*<sup>16</sup> demonstrated that hemorrhagic shock followed by crystalloid resuscitation did not alter the pharmacokinetics but did increase the potency of propofol; hence, the alterations in propofol pharmacokinetics observed with moderate to severe blood loss can be reversed with fluid resuscitation, but the alterations in pharmacodynamics cannot be reversed. This is consistent with the current study in that the increase in end-organ sensitivity induced by hemorrhagic shock cannot be reversed by fluid resuscitation, although the degree of alteration with isoflurane is minimal, in contrast to propofol.

Inhalational anesthetics are known to have different pharmacokinetic properties to those of intravenous anesthetics. Anesthetic uptake itself is the product of three factors: solubility (the blood/gas partition coefficient), CO, and the difference in the alveolar and venous partial pressures.<sup>11</sup> The distribution from blood to each tissue group depends on tissue perfusion and anesthetic solubility (the tissue/blood partition coefficient).<sup>11</sup> It is clear that hemorrhage of 40% of the initial blood volume will influence the uptake and distribution of isoflurane. Hemorrhage greatly decreased CO (table 2), and a reduced passage of blood through the lungs is expected to decrease uptake and increase the alveolar concentration. Hemorrhage leads to decreases in CO and blood volume and results in decreased tissue distributions, especially for muscles and fat. In fact, because rapid increases or decreases in the EtIso/FiIso ratio were observed after 40% bleeding during an increase or decrease in inhalational concentration (fig. 1), an influence of the decrease in CO and blood volume on uptake and tissue distribution of isoflurane was apparently observed. Fluid resuscitation after high-volume blood loss also influences the uptake and distribution of isoflurane, but this effect seems to be complicated. Hydroxyethyl starch infusion equivalent to the withdrawn blood volume increased CO to a greater extent than observed under control conditions (table 2). After hydroxyethyl starch infusion, it is likely that the blood/gas partition coefficient will de-

crease and the tissue/blood (and brain/blood) partition coefficient will increase, because exchange of the circulating blood with hydroxyethyl starch decreases the fat content in blood. Zhou *et al.*<sup>17</sup> reported that hemodilution with normal saline, which induced a 40% decrease in hematocrit, decreases the blood/gas partition coefficient of isoflurane by approximately 22% in humans. In the current study, a slow decrease or a slow increase in the EtIso/FiIso ratio was observed after fluid infusion during a decrease or increase in inhalational concentration, respectively (fig. 1). Hence, although the extent of the changes in anesthetic solubility were not clear, the influence of the increase in CO was greater than that of the decrease in the blood/gas partition coefficient, and uptake through the lungs seemed to increase. Furthermore, tissue uptake of isoflurane also seemed to increase because of the increase in both tissue perfusion and the tissue/blood (and brain/blood) partition coefficient. In addition,  $k_{e0}$ , which is the elimination constant from the effect site and also estimates the onset effect, decreased after 40% bleeding and reversed in value after fluid infusion (table 3). The  $k_{e0}$  value also seemed to be influenced by changes in CO to a greater extent than by changes in the brain/blood partition coefficient, and fluid resuscitation was able to reverse the onset effect of isoflurane.

High-volume blood loss slightly shifted the concentration-effect relation, and decompensated hemorrhagic shock altered the electroencephalographic effect of isoflurane. The mechanism through which hemorrhagic shock increases the end-organ sensitivity of isoflurane is unclear, but several suggestions have been made regarding the extreme increase in end-organ sensitivity of propofol during hemorrhagic shock. Several investigators have demonstrated large increases in circulating  $\beta$ -endorphins during hemorrhage shock in a variety of models,<sup>18-20</sup> and this increase in circulating  $\beta$ -endorphins may lead to an increase of propofol potency. However, DePaeppe *et al.*<sup>21</sup> demonstrated that endorphin antagonism with naloxone does not influence end-organ sensitivity of propofol during hemorrhagic shock in the rat. In a study investigating the influence of hemorrhagic shock on the pharmacokinetics and pharmacodynamics of remifentanyl, Johnson *et al.*<sup>3</sup> reported that administration of remifentanyl ( $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) for 10 min under 1 minimum alveolar concentration of isoflurane clearly decreases the SEF, suggesting that the electroencephalographic effect of isoflurane can be influenced by the presence of opioids. Another potential source of increased end-organ sensitivity to propofol is an increase of unbound propofol; this may be achieved through competitive displacement by other drugs or endogenous substances or by a decrease in the level of plasma proteins.<sup>22,23</sup> Under normal conditions, more than 97% of propofol is bound to plasma proteins and erythrocytes in blood, with an unbound fraction of less than 3%.<sup>24</sup>

Hence, even a small increase in the unbound fraction may increase the end-organ sensitivity of propofol. However, because most isoflurane is carried in fat and water in blood, and only a small percentage of isoflurane is bound to proteins,<sup>25</sup> it seems unlikely that changes in protein binding will alter the end-organ sensitivity of isoflurane. Although further examination of the mechanism is required, we can at least conclude that the pharmacodynamic changes associated with isoflurane during hemorrhagic shock are minimal, and combined with the pharmacokinetic properties, this suggests that control of the hypnotic state in clinical use does not require any special precautions. Johnson *et al.*<sup>3,6,16</sup> performed a series of studies investigating the influence of hemorrhage (and resuscitation) on the pharmacokinetics and pharmacodynamics of several intravenous anesthetics in the presence of isoflurane. Interestingly, they reported that no significant change in the Bispectral Index or SEF values occurred after severe hemorrhage (*i.e.*, both the Bispectral Index and SEF do not decrease beyond that initially produced by isoflurane). These findings also seem to be consistent with the results of the current study.

Several limitations of the current study must be addressed. Although the study was performed using withdrawal of an exact amount of blood to a level at which a decompensated hemorrhagic shock state is expected to be reached, according to our previous studies,<sup>12,15</sup> animals may vary in their degree of metabolic compromise or compensation capacity in response to hemorrhagic shock. Hence, use of an isobaric hemorrhage model<sup>3,6,16</sup> might have been more appropriate to obtain an equivalent degree of metabolic compromise between each animal and to define the decompensated hemorrhagic shock. In addition, we have used isoflurane, which is a moderately soluble anesthetic that is only weakly metabolized, and use of an agent of low or high solubility and/or one that is relatively highly metabolized may give different pharmacokinetic data. Finally, the time dependence of the observed changes in pharmacodynamics was not investigated, and it is possible that the duration of the decompensated hemorrhagic shock state or the period after fluid resuscitation might influence the pharmacodynamics to some extent.

In summary, severe hypovolemia induced by high-volume blood loss alters the electroencephalographic effect of isoflurane at a level at which hemorrhagic shock progresses to a decompensated state, and subsequent fluid resuscitation reverses the delayed onset effect but does not reverse the increase in end-organ sensitivity. However, the pharmacologic changes with isoflurane seem to be minimal, including the pharmacodynamic changes. This is in contrast to several intravenous anesthetics and suggests that the use of an inhala-

tional anesthetic, rather than an intravenous anesthetic, is a relatively easy approach for control of the hypnotic state in patients who have significant blood loss before or during surgery.

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