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Influence of Hypovolemia on the Electroencephalographic Effect of Isoflurane in a Swine Model

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Background: **Hypovolemia alters the effect of several intravenous anesthetics by influencing pharmacokinetics and end-organ sensitivity. The authors investigated the influence of hypovolemia on the effect of an inhalation anesthetic, isoflurane, in a swine hemorrhage model.**

Methods: **Eleven swine were studied. After animal preparation with inhalation of 2% isoflurane anesthesia, the inhalation concentration was decreased to 0.5% and maintained at this level for 25 min before being returned to 2% (control). After 25 min, hypovolemia was induced by removing 14 ml/kg of the initial blood volume *via* an arterial catheter. After a 25-min stabilization period, the inhalation concentration was decreased to 0.5%, maintained at this level for 25 min, and then returned to 2% (20% bleeding). After another 25 min, a further 7 ml/kg blood was collected, and the inhalation concentration was altered as before (30% bleeding). End-tidal isoflurane concentrations and an electroencephalogram were recorded throughout the study. Spectral edge frequency was used as a measure of the isoflurane effect, and pharmacodynamics were characterized using a sigmoidal inhibitory maximal effect model for the spectral edge frequency *versus* end-tidal concentration.**

Results: **There was no significant difference in the effect of isoflurane among the conditions used. Hypovolemia did not shift the concentration–effect relation (the effect site concentration that produced 50% of the maximal effect was 1.2 ± 0.2% under control conditions, 1.2 ± 0.2% with 20% bleeding, and 1.1 ± 0.2% with 30% bleeding).**

Conclusions: **Hypovolemia does not alter the electroencephalographic effect of isoflurane, in contrast to several intravenous anesthetics.**

HYPOVOLEMIA increases the effect of several classes of intravenous anesthetics, including opioids,[1–3] sedative hypnotics,[4–9] benzodiazepines,[8,9] and local anesthetics.[10] These findings have been explained mainly by an increase in drug concentration induced by a reduction in the distribution volume and clearance, and by an increase in end-organ sensitivity. In a clinical situation requiring maintenance of total intravenous anesthesia, these characteristics of intravenous anesthetics sometimes complicate the treatment of patients who have significant blood loss before or during surgery.

Inhalation anesthetics have different pharmacokinetic properties. Uptake from alveoli to blood is restricted by blood solubility (blood/gas partition coefficient) and cardiac output. Only a small amount of an inhalation anesthetic is metabolized, and most is eliminated through exhalation. These pharmacokinetic characteristics suggest that hypovolemia might influence the effect of inhalation anesthetics to a lesser extent than for intravenous anesthetics, although the effects on end-organ sensitivity are unclear. There have been few studies investigating the influence of hypovolemia on the effect of inhalation anesthetics.

We conducted the current study to investigate the influence of hypovolemia induced by blood loss on the electroencephalographic effect of isoflurane. To do so, we assessed the changes in spectral edge frequency and end-tidal isoflurane concentration between 0.5% and 2% inhalation concentrations in the hypovolemic state, which was induced by initial withdrawal of 20% of the blood volume and subsequently a further 10% (for a total of 30%) in a swine model. We hypothesized that hypovolemia would not influence the effect of isoflurane, in contrast to several intravenous anesthetics.

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). Eleven swine (body weight range, 22.5–31.6 kg; mean ± SD, 27.5 ± 3.0 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% inhalation 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 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, 4 lumen; Nihon Kohden, Tokyo, Japan) was 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 re-

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gions 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® electroencephalographic instrument with software version 3.0 (Aspect Medical Systems). Digitized raw electroencephalographic waveform data and processed electroencephalographic values were collected electronically.

Experimental Protocol

After completion of the animal preparation and obtaining baseline measurements, the inhalation 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 20% of the initial blood volume (the total volume was assumed to be 70 ml/kg) over 4 min from the femoral artery 25 min later, and after confirming the stability of the electroencephalogram, the inhalation 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, similar to the control (20% bleeding conditions). A further 10% of the initial blood volume (giving a total of 30% removal of the initial blood volume) was then removed over 2 min, and after a further 25 min, the same inhalation concentration procedure as that described above was performed (30% bleeding conditions). Because hemorrhage of more than 35% of initial blood volume without fluid infusion can induce circulatory collapse in some swine, according to our previous study,[11] we conducted the current study with 30% bleeding as the upper limit to evaluate the electroencephalographic effect of isoflurane. Hematocrit, lactate, and arterial blood gases were measured under all conditions, and heart rate, mean arterial pressure (MAP), central venous pressure, and cardiac output (CO) were recorded at each inhalation 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). We did not choose the Bispectral Index (BIS) for evaluation, because in most animals the BIS value remained at more than 80 under end-tidal 2% isoflurane anesthesia (approximately 1.3 minimum alveolar concentration in swine).[12] Furthermore, some animals did not develop a BIS response after administration of isoflurane, despite having similar end-tidal concentration changes to those in other animals that did show a BIS response. Hence, we judged that the BIS does not adequately evaluate the pharmacodynamic effect of isoflurane in swine, and we therefore chose the SEF as an alternative. 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 (EtIso): $dC_e/dt = (EtIso - C_e)\ k_{e0}$, in which k_{e0} is the elimination constant from the effect site and determines the equilibration between EtIso and C_e. The k_{e0} value was calculated for each pig 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 EtIso values at the respective times. Because plots of the concentration–electroencephalographic effect relation were sigmoidal, an inhibitory sigmoid E_{max} equation (Hill equation)[13] 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 γ 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[14]: $R^2 = 1 - SSE/SST$, where SSE (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 ± 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 significant, the Scheffé F test was performed for multiple comparisons. *P* values less than 0.05 were considered to be statistically significant.

Results

Metabolic and hemodynamic parameters in each state are shown in tables 1 and 2. After removing 20% of the

Table 1. Metabolic Parameters in Each State

	Control	20% Bleeding	30% Bleeding
pH	7.50 ± 0.03	7.52 ± 0.04	7.51 ± 0.04
P_{CO_2}, mmHg	38.5 ± 4.5	34.6 ± 3.5*	34.7 ± 3.7*
P_{O_2}, mmHg	212 ± 41.9	218 ± 51.5	222 ± 44.7
Base excess, mM	6.1 ± 1.4	4.8 ± 2.6*	4.1 ± 2.9*
Lactate, mM	2.0 ± 0.5	2.2 ± 0.7	2.6 ± 1.2
Hematocrit, %	29.8 ± 3.2	33.4 ± 4.8*	31.9 ± 4.5*

* $P < 0.05$, significant difference *vs.* control.

P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

initial blood volume, the partial pressure of carbon dioxide and base excess significantly decreased, and hematocrit increased. Lactate also tended to increase with bleeding. Heart rate, MAP, and CO increased when the inhalation concentration was decreased to 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/FiIso) during a decrease in inhalation concentration from 2% to 0.5% (A) and during an increase in inhalation concentration from 0.5% to 2% (B). The decrease of the EtIso/FiIso ratio was slow after hemorrhage during the phase of concentration decrease, and approximately 25 min were required for this ratio to reach 1.1 in both bleeding states (compared with 18 min under control conditions). The EtIso/FiIso ratio increased more rapidly with increased bleeding in the return phase and reached 0.9; this increase took approximately 9.8 min under control conditions, 6.2 min with

Table 2. Hemodynamic Parameters in Each State

	Control	20% Bleeding	30% Bleeding
HR, beats/min			
2%	121 ± 23	153 ± 44*	198 ± 51†
0.5%	134 ± 15	183 ± 41*‡	218 ± 43†
$2\%_2$	126 ± 32	165 ± 47*	210 ± 50†
MAP, mmHg			
2%	74 ± 12	66 ± 10	63 ± 8*
0.5%	97 ± 9‡	85 ± 10*§	71 ± 8†§
$2\%_2$	79 ± 15	68 ± 11	58 ± 5*
CVP, mmHg			
2%	8.3 ± 1.6	6.6 ± 1.0*	5.7 ± 1.3†
0.5%	7.5 ± 1.1	6.6 ± 1.4	5.7 ± 1.1*
$2\%_2$	8.0 ± 1.3	6.6 ± 1.6*	6.0 ± 0.8*
CO, l/min			
2%	3.0 ± 0.4	2.6 ± 0.5	2.5 ± 0.6*
0.5%	3.5 ± 0.6‡	2.9 ± 0.7*‡	2.6 ± 0.6†
$2\%_2$	3.0 ± 0.4	2.8 ± 0.6	2.5 ± 0.6*

* Significant difference *vs.* control. † Significant differences *vs.* control and 20% bleeding. ‡ Significant difference *vs.* the first 2% state. § Significant differences *vs.* both 2% 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 $2\%_2$, CVP $2\%_2$, HR $2\%_2$, and MAP $2\%_2$ = CO, CVP, HR, and MAP at the second inhalational isoflurane concentration of 2%, respectively.

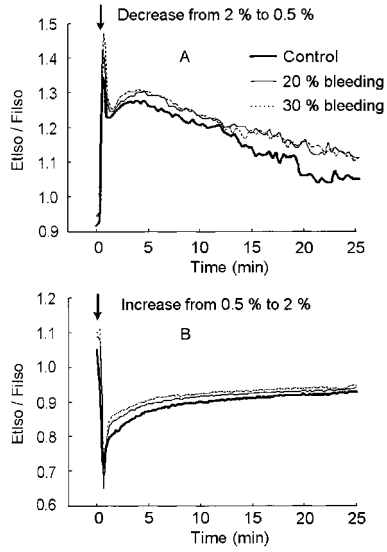

Fig. 1. Changes in the mean ratio of end-tidal isoflurane concentration to inspired isoflurane concentration (EtIso/FiIso) during a decrease in inhalation concentration from 2% to 0.5% (*A*) and during an increase in inhalation concentration from 0.5% to 2% (*B*).

20% bleeding, and 4.5 min with 30% bleeding. Figure 2 shows the time course of both EtIso and SEF for a typical pig. Isoflurane decreased the SEF between inhalation concentrations of 0.5% and 2%, and an increase or decrease in SEF was observed shortly after a respective decrease or increase in EtIso. The pharmacodynamics of isoflurane were studied by correlating the electroencephalographic effect with EtIso. When the SEF values were plotted against EtIso, hysteresis was observed in all animals, as illustrated in figure 3A for the same animal shown in figure 2. The hysteresis was collapsed by estimating the elimination constant from the effect site (k_{e0}), resulting in the effect site concentration–SEF effect relation for isoflurane shown in figure 3B. The individual curves for all animals in each state are shown in figure 4. The correlations of the SEF to the effect site concentration were good in all states, and the correlation coefficients (R^2) were 0.93 ± 0.05 under control conditions, 0.93 ± 0.06 with 20% bleeding, and 0.93 ± 0.07 with 30% bleeding. The EC_{50} values (with 95% confidence intervals) were 1.2 (1.1–1.3) under control conditions,

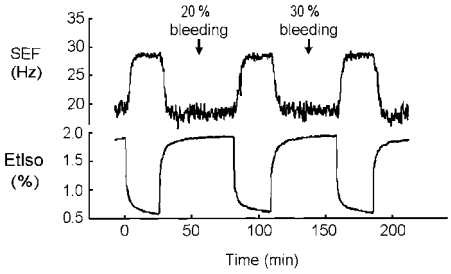

Fig. 2. Changes in spectral edge frequency (SEF) and end-tidal isoflurane concentration (EtIso) during an experiment in a typical pig. *Arrows* show the time points of hemorrhage.

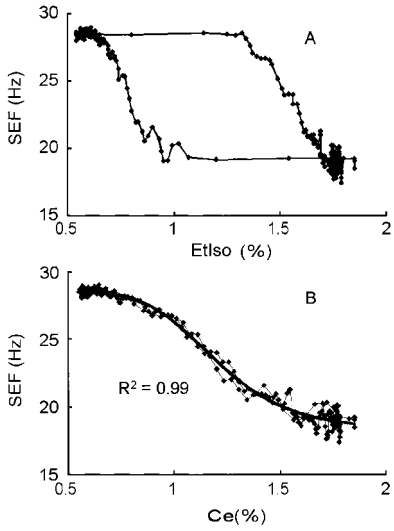

Fig. 3. (*A*) Relation between spectral edge frequency (SEF) and end-tidal isoflurane concentration (EtIso) during a decrease in inhalation concentration from 2% to 0.5% (the lower limb of the loop) and then an increase back to 2% (the upper limb) under control conditions for the same pig shown in figure 2. (*B*) Relation between SEF and effect site isoflurane concentration (C_e) after hysteresis minimization.

1.2 (1.1–1.3) with 20% bleeding, and 1.1 (1.0–1.2) with 30% bleeding. The SEF values (with 95% confidence intervals) at each EC_{50} were 22.6 (21.8–23.3) under control conditions, 22.8 (22.2–23.3) with 20% bleeding, and 22.3 (21.6–23.0) with 30% bleeding. The pharmacodynamic parameters are presented in table 3. k_{e0} and

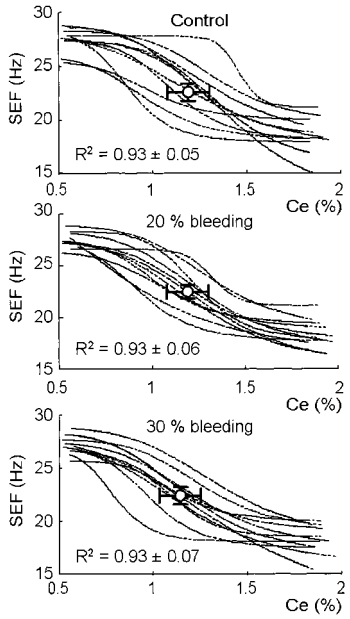

Fig. 4. Individual relations between spectral edge frequency (SEF) and effect site isoflurane concentration (C_e) in each state. *Open circles* are EC_{50} values with 95% confidence intervals. The EC_{50} values (with 95% confidence intervals) were 1.2 (1.1–1.3) under control conditions, 1.2 (1.1–1.3) with 20% bleeding, and 1.1 (1.0–1.2) with 30% bleeding, respectively. R^2 values are correlation coefficients between SEF and C_e.

Table 3. Pharmacodynamic Parameters

	Control	20% Bleeding	30% Bleeding
k_{e0}, min^{-1}	0.44 ± 0.13	0.40 ± 0.05	0.38 ± 0.09
E_0, Hz	27.5 ± 1.1	27.9 ± 1.3	27.4 ± 0.9
E_{max}, Hz	17.7 ± 2.3	17.6 ± 1.8	17.2 ± 2.3
γ	8.1 ± 5.9	6.9 ± 4.0	6.2 ± 1.7
EC_{50}, %	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2

No significant differences were found among the three conditions. E_0 = baseline spectral edge effect level; E_{max} = maximal spectral edge effect; EC_{50} = effect site concentration that produces 50% of the maximal spectral edge effect; γ = a measure of curve steepness; k_{e0} = elimination constant from the effect site.

γ showed a decreasing trend with bleeding, but the differences were not significant ($P = 0.34$ and $P = 0.38$, respectively). Other parameters were quite similar among the different conditions, showing that hemorrhage did not significantly change the effect of isoflurane on SEF.

Discussion

We have investigated the influence of hypovolemia induced by blood loss on the electroencephalographic effect of isoflurane. The results of the current study indicate that hemorrhage, at least to a level of 30% of the initial blood volume, does not alter the electroencephalographic effect of isoflurane. Hemorrhage of 30% of initial blood volume without fluid infusion did not induce circulatory collapse in any animals, and hemorrhagic shock seemed to be compensated. This is consistent with our previous study[11] and also supported by the hemodynamic and metabolic changes observed in the current study. The clinical implication of our study is that, even if severe hypovolemia is induced by surgical bleeding, as long as it is compensated, the hypnotic potential of isoflurane does not change; the end-tidal concentration at steady state is reliable enough to predict the hypnotic depth.

The influence of blood loss on the pharmacologic properties of several intravenous anesthetics has been discussed in many previous reports,[1–9] 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. In studying the influence of blood loss on the pharmacokinetics and pharmacodynamics of propofol, De Paepe *et al.*[5] have demonstrated that moderate blood loss (18 ml/kg) results in a decrease in central compartment clearance and volume and an increase in end-organ sensitivity in the rat. These pharmacologic changes required a 2.5-fold reduction in dose *via* continuous infusion to achieve the same drug effect. Johnson *et al.*[6] have also demonstrated that hemorrhagic

shock shifts the concentration–effect relation to the left, in a study investigating the influence of more 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 previous studies, this group has also demonstrated that hemorrhagic shock alters the pharmacokinetics of fentanyl and remifentanil, resulting in a twofold increase in drug concentrations after equivalent dosing to control and moderately hemorrhaged swine.[2,3] We have recently reported on the influence of fluid infusion associated with blood loss on the pseudo–steady state propofol concentration, using a stepwise hemorrhage and fluid infusion model in swine, and concluded that high-volume blood loss is not adequately managed by fluid infusion and that hypovolemia is induced, leading to a tendency for the plasma propofol concentration to increase.[15] Honan *et al.*[16] have reported that major venous bleeding can induce acute alteration of propofol pharmacokinetics, which was detected by a decrease in BIS during propofol–alfentanil anesthesia. These characteristics of intravenous anesthetics are not only consistent with the clinical practice of reducing the dose for patients who have significant blood loss before or during surgery, but are also consistent with complications in the management of hypovolemic patients who are maintained under total intravenous anesthesia.

Inhalation anesthetics are known to have different pharmacokinetic properties to those of intravenous anesthetics. Because they are delivered through the lung, uptake from alveoli to blood is restricted by blood solubility (blood/gas partition coefficient) and CO. Only a small amount of an inhalation anesthetic is metabolized, and most is eliminated through exhalation. Based on these pharmacokinetic characteristics, we anticipated that hypovolemia would alter the effect of inhalation anesthetics to a lesser extent than for intravenous anesthetics.

It seems likely that hemorrhage should influence the uptake and distribution of isoflurane. 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.[17] Among these three factors, hemorrhage clearly decreased CO (table 2), and a reduced passage of blood through the lungs is expected to decrease uptake and increase the alveolar concentration. The distribution from blood to each tissue group depends on tissue perfusion and anesthetic solubility (the tissue/blood partition coefficient). Hemorrhage leads to decreases in CO and blood volume and results in decreased tissue perfusion, especially for muscles and fat. In the current study, because rapid increases in the EtIso/FiIso ratio were observed with bleeding during an increase in inhalation concentration from 0.5% to 2% (fig. 1B), an influence of the decrease in CO and blood volume on uptake or tissue distribution of isoflurane or both was apparently observed. However, the blood isoflurane concentration and the effect site isoflurane concentration did not seem to change after hemorrhage, because neither EtIso nor SEF changed after each hemorrhage step with 2% isoflurane. In addition, because isoflurane does not hinder dynamic cerebral autoregulation[18] and MAP was maintained within approximately 20% of its control value (table 2), cerebral blood flow seemed to be maintained during the experiments.

Hemorrhage did not shift the concentration–effect relation, and hypovolemia did not alter the electroencephalographic effect of isoflurane. Several investigators have demonstrated large increases in circulating β endorphins during hemorrhage shock in a variety of models.[19–21] Although isoflurane interaction with endogenous opioids can alter the response to noxious stimuli, the electroencephalographic effect of isoflurane may not necessarily be influenced in the presence of opioids.[22,23] Hence, we cannot conclude from our results that hemorrhage does not alter the anesthetic potential of isoflurane in response to noxious stimuli, but we can conclude that hemorrhage does not alter the hypnotic potential of isoflurane.

Several limitations of the current study must be addressed. Because the study was performed under conditions of compensated hemorrhagic shock, we were unable to assess the influence of more severe hypovolemia, under which a decompensated hemorrhagic shock state may be reached, on the electroencephalographic effect of isoflurane. We successively performed a decrease and subsequent return of the inhalation concentration to control levels, both before and after a two-step hemorrhage procedure. Because the durations of exposure to isoflurane were different in each state, the tissue partial pressure would be variable, and this might have influenced our results, especially in the recovery phase.[17] In fact, a slow decrease of the EtIso/FiIso ratio during the decrease in inhalation concentration from 2% to 0.5% was observed after hemorrhage (fig. 1A), despite decreases in CO and blood volume. In addition, we used isoflurane, which is a moderately soluble anesthetic that is only weakly metabolized. If a highly soluble or relatively highly metabolized agent was used, the results might be different. We also note that unresuscitated hemorrhage is not typical of clinical practice. Fluid resuscitation, blood transfusion, or both are usually performed before anesthetic induction, and fluid infusion associated with high volume blood loss may change the solubility (the blood/gas partition coefficient) of inhalation anesthetics. Finally, from an ethical perspective, decreasing the anesthesia to 0.5% isoflurane as the minimum dose was important to assure sedation. Discontinuing isoflurane inhalation would have allowed a more accurate effect site concentration–effect curve to be obtained, but such a procedure was ethically unacceptable.

In summary, hypovolemia induced by hemorrhage does not alter the electroencephalographic effect of isoflurane, at least if hemorrhagic shock is compensated, and therefore, the end-tidal concentration at steady state may be useful for predicting the hypnotic level of isoflurane, even with severe hypovolemia. The clinical implication of our study is that when controlling the hypnotic state for patients who have significant blood loss before or during surgery, the use of an inhalation anesthetic, rather than an intravenous anesthetic, seems to be appropriate.

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