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# *Influence of Hemorrhagic Shock Followed by Crystalloid Resuscitation on Propofol*

## *A Pharmacokinetic and Pharmacodynamic Analysis*

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***Background:*** **Previous work has demonstrated that ongoing hemorrhagic shock dramatically alters the distribution, clearance, and potency of propofol. Whether volume resuscitation after hemorrhagic shock restores drug behavior to baseline pharmacokinetics and pharmacodynamics remains unclear. This is particularly relevant because patients suffering from hemorrhagic shock are typically resuscitated before surgery. To investigate this, the authors studied the influence of an isobaric bleed followed by crystalloid resuscitation on the pharmacokinetics and pharmacodynamics of propofol in a swine model. The hypothesis was that hemorrhagic shock followed by resuscitation would not significantly alter the pharmacokinetics but would influence the pharmacodynamics of propofol.**

***Methods:*** **After approval from the Animal Care Committee, 16 swine were randomly assigned to control and shock-resuscitation groups. Swine randomized to the shock-resuscitation group were bled to a mean arterial blood pressure of 40 mm Hg over a 20-min period and held there by further blood removal until 42 ml/kg of blood had been removed. Subsequently, animals were resuscitated with lactated Ringer's solution to maintain a mean arterial blood pressure of 70 mm Hg for 60 min. After resuscitation, propofol (750 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused for 10 min. The control group underwent a sham hemorrhage and resuscitation and received propofol at the same dose and approximate time as the shock-resuscitation group. Arterial samples (20 from each animal) were collected at frequent intervals until 180 min after the infusion began and were analyzed to determine drug concentrations. Pharmacokinetic parameters for each group were estimated using a three-compartment model. The electroencephalogram Bispectral Index Scale was used as a measure of drug effect. Pharmacodynamics were characterized using a sigmoid inhibitory maximal effect model.**

***Results:*** **The raw data demonstrated minimal differences in the mean plasma propofol concentrations between groups. The compartment analysis revealed some subtle differences between groups in the central and slow equilibrating volumes, but the differences were not significant. Hemorrhagic shock followed by resuscitation shifted the concentration effect relationship to the left, demonstrating a 1.5-fold decrease in the effect-site concentration required to achieve 50% of the maximal effect in the Bispectral Index Scale.**

***Conclusions:*** **Hemorrhagic shock followed by resuscitation with lactated Ringer's solution did not alter the pharmacokinetics but did increase the potency of propofol. These results demonstrate that alterations in propofol pharmacokinetics observed in moderate to severe blood loss can be reversed with resuscitation. These results suggest that a modest reduction in propofol is prudent to achieve a desired drug effect after resuscitation from severe hemorrhagic shock.**

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HEMORRHAGIC shock alters both the pharmacokinetics and pharmacodynamics of propofol.[1,2] Previous work has demonstrated that blood loss alters the pharmacology of propofol such that equivalent dosing leads to higher drug concentrations and prolonged drug effect in the setting of moderate to severe blood loss when compared to euvolemic, normotensive conditions. These findings are consistent with the clinical practice of reducing the dose of intravenous anesthetics for patients who have significant blood loss before or during surgery.

Using compartmental models, previous work in our laboratory[2] and by others[1] studying the influence of blood loss on the pharmacokinetics and pharmacodynamics of propofol have demonstrated that moderate blood loss (up to 30 ml/kg) results in a decrease in compartmental volumes or clearances and an increase in end-organ sensitivity in both rodent and swine hemorrhage models. These pharmacokinetic and pharmacodynamic changes resulted in up to a five-fold reduction in dose required to achieve the same drug effect. A decrease in blood volume[3] and cardiac output[4,5] along with compensatory changes in regional blood flow are the likely physiologic mechanisms explaining the pharmacokinetic changes. Mechanisms to describe the increase in end-organ sensitivity to propofol after blood loss have not been described but may be a consequence of the metabolic derangements associated with severe hemorrhagic shock.

Whether or not volume resuscitation after hemorrhagic shock restores drug disposition and effect to baseline remains unclear. Previous studies in our laboratory and elsewhere have used controlled, unresuscitated hemorrhagic shock models to study the influence of

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blood loss on drug behavior. These models, however, do not reflect the clinical practice of providing some degree of resuscitation before the administration of an anesthetic in patients suffering from hemorrhagic shock. To investigate this, we studied the influence of hemorrhagic shock followed by partial resuscitation with crystalloid on the pharmacokinetics and pharmacodynamics of propofol in a swine model. Based on the premise that resuscitation will restore cardiac output and systemic blood flow but not immediately change the metabolic disturbances that lead to increased end-organ sensitivity, our hypotheses were that hemorrhagic shock followed by resuscitation would restore near normal pharmacokinetics but not reverse the shock-induced pharmacodynamic changes previously observed in propofol after hemorrhagic shock.

## Methods and Materials

### *Experimental Design*

Experiments were performed on commercial farm-bred swine of either sex. The study was approved by the Institutional Animal Care and Use Committee at the University of Utah. Animals were randomly assigned to either an isobaric hemorrhage-resuscitation or a control group (n = 8 for each group). In the shock-resuscitation group, animals were bled to a shock state, resuscitated with lactated Ringer's solution, and then administered a 10 min propofol infusion. In the control group, animals were instrumented in an identical fashion to the shock-resuscitation group and maintained in an anesthetized, ventilated state for a sham hemorrhage and resuscitation period before receiving the propofol infusion. This was done to ensure that both groups would receive the propofol infusion after near-equivalent times receiving anesthesia.

### *Animal Preparation*

Swine weighing 36.8 ± 1.2 kg (mean ± SEM) were commercially obtained and quarantined for 6 days in a temperature and light controlled environment. Animals had access to food and water *ad libitum*. Anesthesia was induced with tiletamine HCl 2.3 mg/kg, zolazepam 2.3 mg/kg, ketamine 2.3 mg/kg, and xylazine 2.3 mg/kg as described by Ko *et al.*[6] for pigs as an intramuscular injection. Intravascular access was obtained from an ear vein. A continuous crystalloid infusion with lactated Ringer's solution was administered through the peripheral ear vein to meet insensible fluid and electrolyte losses according to the following set of rules: 4 $ml \cdot kg^{-1} \cdot h^{-1}$ for the first 10 kg, 2 $ml \cdot kg^{-1} \cdot h^{-1}$ for the next 10–20 kg, and 1 $ml \cdot kg^{-1} \cdot h^{-1}$ for each kg above 20 kg.

Each trachea was then intubated and the lungs were mechanically ventilated. Initial ventilator settings were a tidal volume of 8 to 10 ml/kg, a respiratory rate of 20 breaths/min, a $F_{IO_2}$ of 100%, and no positive end-expiratory pressure. Tissue oxygenation was monitored using continuous pulse oximetry placed on the tongue or ear. Ventilation was monitored using an inspired/expired gas analyzer that measured oxygen, carbon dioxide, and isoflurane concentrations. Ventilator settings were adjusted as needed to keep the pulse oximetry greater than 95% and the end-tidal $CO_2$ at 38 ± 4 mm Hg. Once satisfactory ventilator settings were established, a baseline arterial blood gas was obtained. Ventilator settings were adjusted further if needed to maintain the arterial $P_{CO_2}$ at 40 ± 4 mm Hg.

A continuous level of anesthesia was achieved with isoflurane and intermittent boluses of pancuronium (0.1 mg/kg). Expired isoflurane concentrations were monitored and kept at 1.0 MAC equivalent for swine (an end-tidal isoflurane concentration of 1.6%).[7] Subcutaneous electrocardiograph electrodes were placed and the electrocardiogram was monitored throughout the study.

The left femoral artery was cannulated with a 16-gauge arterial sheath to monitor arterial blood pressure and heart rate continuously. The right femoral artery was cannulated with a 16-gauge arterial sheath for blood removal and subsequent reinfusion. An internal jugular vein was cannulated with a pulmonary artery catheter for intermittent measurements of central venous pressure, pulmonary capillary wedge pressure, and thermodilution estimates of cardiac output. Colonic temperatures were monitored and maintained at 37°C throughout the study with a heating/cooling blanket and heating lamps as needed. Once access to the vascular compartment was obtained, each animal was anticoagulated with an intravenous bolus injection of heparin (100 units per kilogram of body weight). Cardiac index and systemic vascular resistance index were calculated by estimating the body surface area according to the following: body surface area = $(K^*(\text{weight}^{2/3}))/100\ m^2$, where K, a species constant, is 9 for swine;[8] cardiac index = cardiac output/body surface area; and systemic vascular resistance index = systemic vascular resistance/body surface area.

Instrumentation for electroencephalic monitoring was accomplished by preparing the skin over the frontooccipital regions bilaterally and placing four cutaneous electrodes. Four channels of the electroencephalogram were amplified and digitally recorded using an Aspect A1000 electroencephalogram machine (Aspect Medical, Newton, MA). Digitized raw electroencephalographic waveform data and Bispectral Index Scale (BIS) values were collected electronically.

### *Hemorrhage Resuscitation Protocol*

After instrumentation, animals underwent a 30-min stabilization period before initiating the hemorrhage resuscitation protocol. Once in the stabilization period,

the isoflurane was reduced to 0.8% and maintained there for the remainder of the experiment. After the stabilization period, unbled control animals underwent a time controlled sham hemorrhage resuscitation period. The duration of this period was determined by the time required to reach the target hemorrhage and resuscitation end point in the most recent animal assigned to the experimental group.

The hemorrhage resuscitation protocol was designed to ensure that each animal was at an equivalent degree of metabolic compromise from hemorrhagic shock followed by an equivalent duration of partial resuscitation before initiating the propofol infusion. This was accomplished by using an isobaric hemorrhage model as described by Wiggers[9] followed by resuscitation with lactated Ringer's solution.

Animal were bled *via* an arterial line feeding through a roller pump. The roller pump was controlled by a computer. Shed blood was stored in a reservoir placed on a scale. Shed blood volume was measured by weight. *Via* a second arterial line, mean arterial blood pressure (MABP) was continuously acquired by the computer controlling the roller pump. Blood was removed at a rate required to achieve a linear decrease in the MABP to 40 mm Hg over 20 min. Blood was then removed or reinfused by the servocontrolled roller pump to maintain the MABP at 40 mm Hg.

The compensatory phase of hemorrhagic shock was defined as the time during which blood had to be removed to maintain the MABP at 40 mm Hg. The decompensatory phase of hemorrhagic shock was defined as the time period during which blood had to be reinfused to maintain the MABP at 40 mm Hg. The peak shed blood volume was defined as the maximum amount of blood removed during the isobaric hemorrhage process.

Upon reaching the peak shed blood volume during the isobaric hemorrhage, the target MABP was changed from 40 to 70 mm Hg. The shed blood volume stored in a reservoir placed on the scale was replaced with a reservoir of lactated Ringer's solution. Lactated Ringer's solution was infused to maintain the MABP at 70 mm Hg for 60 min.

The arterial blood pressures were measured with a pressure transducer (Utah Medical, Midvale, UT). A computerized data acquisition system recorded the MABP, systolic and diastolic arterial pressures, heart rate, and shed blood volume or resuscitation volume every 5 s.

Arterial blood samples for determining pH, $P_{O_2}$, $P_{CO_2}$, bicarbonate, glucose, potassium, hematocrit, base excess, glucose, and lactate were measured using blood gas and chemistry analyzer (Model Number ABL 725; Radiometer America, Westlake, OH). Samples were obtained before hemorrhage, after hemorrhage, after resuscitation just before the propofol infusion, and on completing the propofol infusion. To assess the impact of the propofol infusion on hemodynamic and metabolic parameters, measurements collected after resuscitation and after the propofol infusion were compared between groups over time using a repeated measures analysis of variance. A $P$ value less than 0.05 was considered significant.

*Propofol Administration and Assay*

After resuscitation, propofol 750 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was infused for 10 min intravenously using a syringe pump (Medfusion 2010I; Medex Inc, Duluth, GA). The dose of 750 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was based on previous work in our laboratory to produce a reliable decrease in electroencephalographic measures of brain activity in unbled swine.[10] At lower doses, some swine would not develop a consistent response to a brief infusion of propofol. During and after the propofol infusion, the roller pump was turned off so that no additional lactated Ringer's solution was infused during the time period when propofol samples were collected. Arterial blood samples (3 ml) were obtained at preset intervals, with more rapid sampling during the infusion and immediately after termination of the infusion. A baseline sample was collected before the infusion. Samples were collected at 2, 4, 6, 8, 10, 11, 12, 13, 14, 15, 17.5, 20, 25, 30, 45, 60, 90, 120, and 180 min after the start of the infusion.

Propofol concentrations were determined by using a gas chromatography mass spectrometer technique with selected ion monitoring as described by Ibrahim *et al.*[11] The detection limit was 50 ng/ml. Coefficients of variation were 8%, 5%, and 4% for interday and 6%, 5%, and 4% for intraday quality control samples at 0.02, 0.5, and 4 $\mu$g/ml.

*Pharmacokinetic Analysis*

The concentration *versus* time data for both groups were analyzed using several techniques. First, individual pharmacokinetic parameters were estimated for each animal subject. Second, an exploration of pharmacokinetic parameter-covariate relationships was made. Third, the control and shock-resuscitation groups were combined to build a population model for nonlinear mixed effects model analysis. Covariates demonstrating a strong correlation with pharmacokinetic parameters were introduced into the population model in an effort to improve the ability of the model to predict propofol plasma concentrations.

*Individual Pharmacokinetic Parameter Estimates*

The concentration *versus* time data were used to estimate pharmacokinetic parameters for a three-compartment model for each animal subject using pharmacokinetic modeling software (NONMEM, Version V; University of California, licensed and distributed by Globomax LLC, Hanover, MD). Estimates of the triexponential equation were parameterized in terms of compartment volumes and clearances. A preliminary comparison of compartment volumes and clearances was

made between groups with an unpaired two-tailed Student *t* test. Because six comparisons were made in this analysis, *P* values of less than 0.0083 were considered significant to maintain the probability of a type I error at 0.05.

*Exploration of Parameter-Covariate Relationships*

Previous work in our laboratory investigating the influence of blood loss on the pharmacokinetics of intravenous opioids and sedative hypnotics has demonstrated that shed blood volume and cardiac index are likely to develop a strong relationship to pharmacokinetic parameters.[2,12] Hence, individual pharmacokinetic parameter estimates were regressed independently on group assignment, shed blood volume, resuscitation volume, and cardiac index as described by Maitre el al.[13] This step was intended to identify useful relationships between model parameters and covariates and to characterize the shape of these relationships.

*Nonlinear Mixed Effects Pharmacokinetic Model Analysis*

Propofol concentration *versus* time data for both the shock-resuscitation and control groups were combined and used to construct a single three compartment population pharmacokinetic model using NONMEM. Data were analyzed to provide an estimate of typical values for the population pharmacokinetic parameters and an estimate of interindividual variability of parameters. We have previously reported the modeling and data analysis techniques used in this analysis.[2,12] The performance of the population model was evaluated in terms of its ability to predict individual animal plasma propofol concentrations. Performance parameters included a measure of accuracy (median absolute weighted residual), bias (median weighted residual), and visual assessment of measured *versus* predicted propofol concentrations and the measured over predicted plasma propofol concentrations over time.

After obtaining the best population model without covariates (simple model), the influence of covariates such as group assignment, shed blood volume, resuscitation volume, and cardiac index on the population model performance were evaluated. Guided by the regression analysis exploring the relationship between model parameters (volumes and clearances) and covariates, a revised population model was built in a stepwise fashion. Covariates were used to modify model parameters and the resulting expanded model was examined for significant improvement. Comparisons were made between covariate expanded models and the simple model using a log likelihood ratio test. This test compared the objective function ($-2 \times$ log likelihood) between models. Expansion of the simple population model by one covariate-pharmacokinetic relationship increased the degrees of freedom for the population model by one. Based on a chi-squared distribution for differences in the degrees of freedom, a decrease in the objective function of at least 4, 6, 8, or 10 was viewed as sufficient justification to include an additional parameter in the model for differences in the degrees of freedom of 1, 2, 3, or 4, respectively. Performance parameters were generated for each model to assess the extent of the model improvement.

*Pharmacodynamic Analysis*

The pharmacologic effect of propofol was characterized by examining the influence of propofol on the BIS value. The BIS values were calculated using the Aspect A1000 machine, software version 3.1. BIS values were recorded when arterial samples were collected for propofol assay. One concern is that hemorrhagic shock followed by resuscitation during an isoflurane anesthetic, in the absence of propofol would alter the BIS values. A set of control experiments (n = 2) were performed to assess the impact of isobaric hemorrhage to the peak shed blood volume followed by a 60 min partial resuscitation with lactated Ringer's solution on the BIS value.

The pharmacodynamic analysis was performed in three steps.

1) Plots of the raw data (plasma propofol concentrations *versus* BIS) were made for each individual animal subject and the hysteresis between drug concentration and effect noted.

2) Because plots of the concentration-effect relationship were sigmoid in shape, an inhibitory effect sigmoid model (*i.e.*, Hill equation) was used to model the relationship parametrically.[14] Using pharmacodynamic modeling software (WinNonLin, Version 3.1, Pharsight Corporation, Chelsea, MI), the parameters in the equation:

$$E = E_0 - (E_0 \cdot C_e^{\gamma}/(C_e^{\gamma} + C_{50}^{\gamma})) \quad (1)$$

where E is the predicted effect, $E_0$ is the baseline effect value, $C_e$ is the effect-site concentration, $\gamma$ is a measure of curve steepness, and $C_{50}$ is the plasma concentration that produces 50% of maximal effect, were fit to each individual animal. This analysis yielded a set of pharmacodynamic parameters and an effect-site concentration-effect (BIS) curve for each individual animal. These plots were reviewed to ensure that the apparent effect-site concentration *versus* BIS data represented a collapsing of the hysteresis noted in the raw plasma propofol concentration *versus* BIS data.

3) Using individual pharmacodynamic parameters, model estimates of the effect-site concentration *versus* drug effect were plotted over a range of 1 to 20 $\mu$g/ml for each animal. Individual pharmacodynamic parameters from the shock and control groups were compared with an unpaired two-tailed Student *t* test. Because four comparisons were made in this analysis, *P* values of less

than 0.0125 were considered significant to maintain the probability of a type I error at 0.05.

All data throughout the results section are presented as mean ± SEM.

### *Nonlinear Mixed Effects Pharmacodynamic Model Analysis*

BIS *versus* time data for both the shock-resuscitation and control groups were combined and used to construct a single, inhibitory effect sigmoid model using mixed effects population modeling software (WinNonMix Professional, Version 2.0.1, Pharsight Corporation, Chelsea, MI). Results from the two stage pharmacodynamic analysis were used to provide an estimate of typical values for the population pharmacodynamic parameters. The population model was linked to the pharmacokinetic parameters previously estimated in the two-stage analysis. The performance of the population model was evaluated in terms of its ability to predict individual animal BIS values.

After obtaining the best population model without covariates (simple model), the influence of group assignment on the population model performance was evaluated. A revised population model was built in a stepwise fashion in which the effect of group assignment on each model parameter was incorporated into the model and the resulting expanded model was examined for significant improvement. Results from the log likelihood ratio test and performance parameters as previously described in the population pharmacokinetic model analysis were used to assess the extent of model improvement.

### *Computer Simulations*

Computer simulations using pharmacokinetic and pharmacodynamic models from the two-stage analysis for each study group were performed to illustrate the influence of blood loss and resuscitation on the pharmacologic behavior of propofol in swine. The first simulation compared differences in the effect-site concentration and BIS between the shock-resuscitation and control models after a bolus (4 mg/kg body weight) and a continuous infusion (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of propofol. Simulation doses were selected to achieve an effect-site concentration near the $C_{50}$ for the control pharmacokinetic/pharmacodynamic model. The second simulation determined the total dose required to deliver a 1 h computer controlled infusion targeted to the $C_{50}$ for both control and shock-resuscitation group models. Simulations were performed using drug infusion simulation software (STANPUMP, Stanford University, Palo Alto, CA). Linear pharmacokinetics were assumed across propofol doses.

## Results

### *Hemorrhage Resuscitation Protocol*

Animals subjected to an isobaric hemorrhage targeted to maintain a MABP of 40 mm Hg required 94 ± 12 min to reach their respective peak shed blood volumes (42 ± 2 ml/kg). Hemorrhaged animals required 59 ± 6 ml/kg of lactated Ringer's solution to maintain a target MABP of 70 mm Hg for 60 min. One animal in the shock-resuscitation group was not resuscitated according to the study protocol and was removed from the analysis. Animals in the control group underwent a sham hemorrhage period of 93 ± 10 min and a sham resuscitation period of 60 min. An example of the typical changes in blood pressure, shed blood volume, resuscitation volume, and propofol concentration over time is presented in fig. 1.

Before initiating the hemorrhage-resuscitation protocol, there was no difference in the hemodynamic and metabolic profiles between the shock-resuscitation and control groups. Bled animals developed a hemodynamic and metabolic profile consistent with hemorrhage shock to include an increase in heart rate, plasma lactate concentrations, and systemic vascular resistance index and a decrease in central venous pressure, cardiac index, arterial pH, and base excess (data not shown). Crystalloid resuscitation led to a return of the central venous pressure, cardiac index, and systemic vascular resistance index to near those values observed in the control group. However, the heart rate and plasma lactate values remained increased, the arterial pH and base excess remained decreased, and the hematocrit dropped in the shock-resuscitation group after resuscitation.

### *Effect of Propofol on Hemodynamic and Metabolic Parameters*

The 10 min propofol infusion produced a larger decrease in the heart rate, MABP, and cardiac index in the shock-resuscitation group than in the control group (table 1). During the propofol infusion, the central venous pressure increased but there was no difference between groups. The systemic vascular resistance index decreased with the propofol infusion, but there was no difference between groups.

During the 10-min propofol infusion, the arterial pH and the base excess increased in the shock-resuscitation group and decreased in the control group. Hematocrit developed a larger decrease in the shock-resuscitation group than in the control group. Changes in plasma lactate and glucose concentrations over the duration of the infusion were not significant.

### *Pharmacokinetic Analysis*

The infusion of propofol administered in this protocol resulted in concentration *versus* time curves characteristic of brief intravenous infusion of a sedative hypnotic exhibiting a rapid distribution phase followed by a

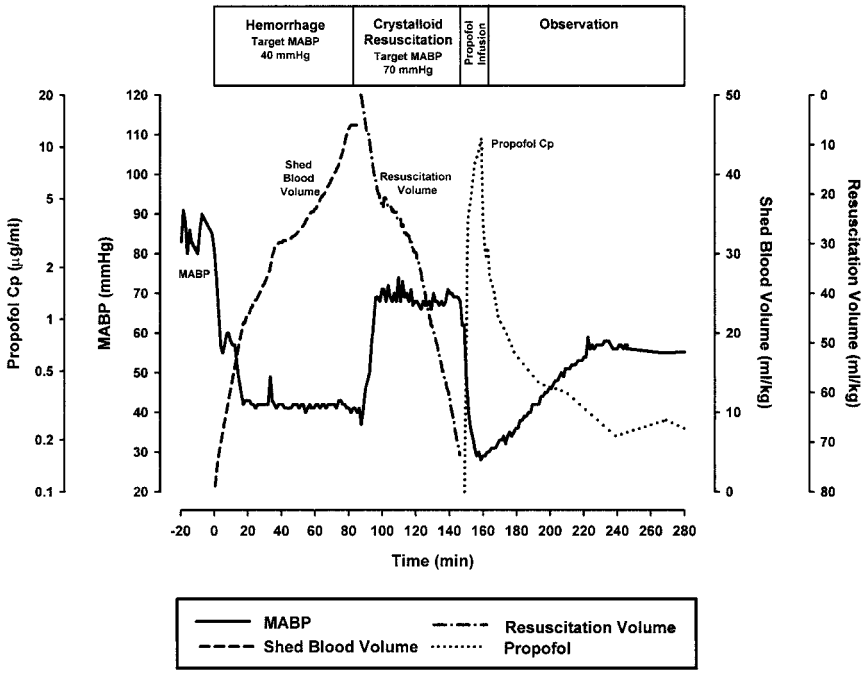


**Fig. 1. Typical time course for the mean arterial blood pressure (*solid line*), shed blood volume (*dashed line*), crystalloid resuscitation volume (*dash-dot line*), and propofol plasma concentration (*dotted line*) during the study period.**

slower elimination phase. Mean and individual propofol concentrations in the shock-resuscitation and control groups are presented in figure 2. Visual inspection of the raw data revealed no appreciable difference in the plasma propofol concentrations between groups throughout the experiment. The peak concentrations on completion of the 10 min propofol infusion were 18.1 ± 3.0 and 16.6 ± 1.9 μg/ml for the shock-resuscitation and control groups respectively. The 95% confidence interval of the mean difference between groups ranged from −5.7 to 8.6 μg/ml.

The raw concentration *versus* time data were well described by a three-compartment model. A set of pharmacokinetic parameters was estimated from the plasma propofol concentration *versus* time data for each individual animal. A summary of the pharmacokinetic parameter estimates by group using the two-stage method is presented in table 2. Although the central compartment was smaller and the slowly equilibrating peripheral compartment was larger, a comparison of the pharmacokinetic parameters between the control and shock-resuscitations groups revealed no significant differences between groups.

### *Nonlinear Mixed Effects Pharmacokinetic Model Population Analysis*

Plots of individual pharmacokinetic parameters *versus* the covariates shed blood volume, resuscitation volume, and cardiac index revealed several potentially useful relationships. The most pronounced relations were be-

**Table 1. Hemodynamic and Metabolic Parameters After Resuscitation After Hemorrhagic Shock, and After Propofol Infusion**

| | Hemorrhage Followed by Crystalloid Resuscitation | | Upon Completion of the Propofol Infusion | |
|---|---|---|---|---|
| Parameter | Control Group | Hemorrhage Resuscitation Group | Control Group | Hemorrhage Resuscitation Group |
| Heart Rate (beats/min) | 113 ± 5 | 155 ± 15 | 101 ± 5 | 105 ± 6* |
| Central Venous Pressure (mm Hg) | 6 ± 1 | 6 ± 1 | 7 ± 1 | 8 ± 1 |
| Pulmonary Artery Occlusion Pressure (mm Hg) | 6 ± 1 | 7 ± 1 | 7 ± 1 | 6 ± 1 |
| Cardiac Index ($L \cdot min^{-1} \cdot m^2$) | 4.8 ± 0.2 | 5.0 ± 0.5 | 4.6 ± 0.2 | 3.3 ± 0.3* |
| Mean Arterial Blood Pressure (mm Hg) | 102 ± 4 | 70 ± 2 | 79 ± 3 | 31 ± 3† |
| Systemic Vascular Resistance Index ($dynes \cdot sec \cdot cm^{-1} \cdot m^2$) | 1601 ± 74 | 1096 ± 162 | 1252 ± 64 | 599 ± 68 |
| Arterial pH | 7.511 ± 0.018 | 7.324 ± 0.021 | 7.481 ± 0.021 | 7.385 ± 0.019* |
| Base Excess (mmol/L) | 8.6 ± 1.0 | −1.7 ± 1.1 | 7.5 ± 1.0 | −0.6 ± 0.9* |
| Plasma Lactate (mmol/L) | 2.0 ± 0.3 | 9.7 ± 0.9 | 2.1 ± 0.3 | 8.9 ± 0.9 |
| Plasma Glucose (mg/dL) | 138 ± 10 | 146 ± 25 | 142 ± 11 | 143 ± 22 |
| Hematocrit | 36 ± 1 | 25 ± 2 | 36 ± 2 | 19 ± 1* |

Data are presented as mean ± standard error of the mean.

* $P < 0.05$ for a repeated measures analysis of variance between groups over the duration of the propofol infusion.

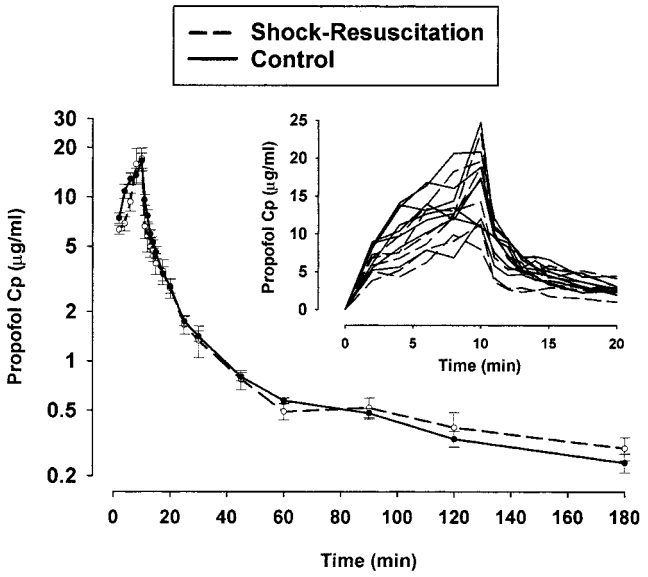


**Fig. 2. Mean propofol plasma concentration *versus* time data. The solid lines represent the plasma concentrations for control animals and the dashed lines represent the plasma concentrations for shock-resuscitation animals. Error bars represent the SEM. Individual propofol plasma concentration *versus* time data are presented in the inset graph over the first 20 min after the start of the propofol infusion.**

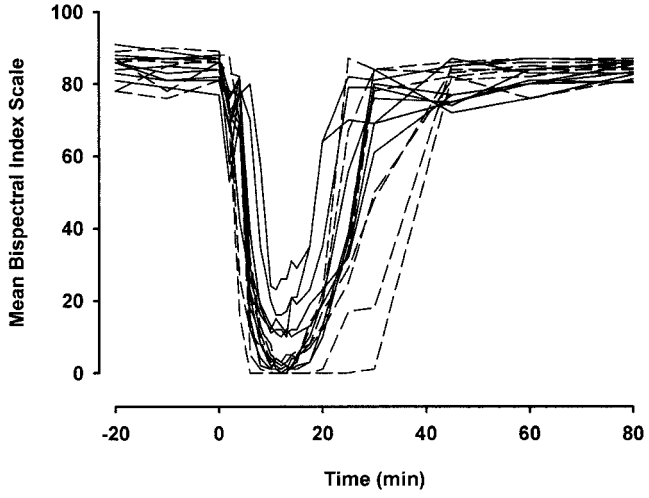


**Fig. 3. Mean bispectral index scale changes *versus* time during and after the propofol infusion for shock-resuscitation and control animals. The solid lines represent the bispectral index scale measurements for the control animals and the dashed lines represent the bispectral index scale measurements for the shock-resuscitation animals. Error bars represent the SEM.**

tween the compartment volumes and shed blood volume, the compartment volumes and resuscitation volume, and the central compartment volume and clearance and cardiac index.

A population pharmacokinetic (three-compartment) model was successfully built using the concentration *versus* time data from the combined shock-resuscitation and control groups. Scaling the population model to group assignment or hemodynamic parameters such as shed blood volume, resuscitation volume, or cardiac index did not improve model performance.

*Pharmacodynamic Analysis*

In a series of pilot studies (N = 2) aimed at demonstrating that the shock resuscitation protocol employed in this study had no effect on the BIS, animals were subjected to the isobaric hemorrhage and resuscitation protocol but did not receive a propofol infusion. There was no change in the BIS throughout the study period.

All animals receiving propofol developed a measurable response in the BIS. The 750 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusion for 10 min produced a decrease in the BIS that returned to baseline within 40 min of the infusion (fig. 3). There was no difference in the BIS between groups before starting the propofol infusion (85 ± 1 and 84 ± 1 for the shock-resuscitation and control groups, respectively). The onset time of the propofol-induced decrease in the BIS was similar between the control and shock-resuscitation groups. Subsequently, the shock-resuscitation group developed a lower BIS score and a slower return to baseline in the first 20 min after completion of the 10 min propofol infusion.

Using an inhibitory effect sigmoid model, a set of pharmacodynamic parameters was successfully estimated from the raw concentration *versus* effect (BIS) data for each individual animal. A comparison of the pharmacodynamic parameter estimates by group using the two stage method is presented in table 3. $E_0$, $\gamma$, and the $k_{eo}$ (the elimination constant from the effect-site compartment) were similar between groups. The $C_{50}$ was 1.5-fold less in the shock-resuscitation group. Plots

**Table 2. Summary of Two-Stage Pharmacokinetic Parameter Estimates by Group**

| Parameter | Control Group | Shock-Resuscitation Group | *P* value |
|---|---|---|---|
| Volumes | | | |
| Central Compartment ($V_1$) | 3.9 ± 0.5 | 2.5 ± 0.6 | 0.067 |
| Rapidly Equilibrating Peripheral Compartment ($V_2$) | 5.5 ± 1.1 | 8.1 ± 2.0 | 0.239 |
| Slowly Equilibrating Peripheral Compartment ($V_3$) | 56.8 ± 10.7 | 104.1 ± 17.5 | 0.024 |
| Clearance (liters/min) | | | |
| Elimination Clearance ($Cl_1$) | 1.0 ± 0.1 | 1.0 ± 0.1 | 0.779 |
| Fast Distribution Clearance ($Cl_2$) | 1.4 ± 0.4 | 2.3 ± 0.5 | 0.143 |
| Slow Distribution Clearance ($Cl_3$) | 0.7 ± 0.1 | 0.9 ± 0.1 | 0.057 |

Data are presented as mean ± standard error of the mean. $P < 0.0083$ is considered significant.

**Table 3. Summary of Two Stage Pharmacodynamic Parameter Estimates by Group**

| Parameter | Control Group | Shock-Resuscitation Group | *P* Values |
|---|---|---|---|
| $E_0$ | 81 ± 2 | 84 ± 1 | 0.086 |
| $\gamma$ | 5.2 ± 0.7 | 7.5 ± 1.7 | 0.220 |
| $C_{50}$ ($\mu$g/ml) | 5.0 ± 0.4 | 3.4 ± 0.4 | 0.024 |
| $k_{e0}$ | 0.13 ± 0.01 | 0.24 ± 0.13 | 0.346 |

Data are presented as mean ± standard error of the mean. $P < 0.0125$ is considered significant.

$C_{50}$ = effect-site concentration that produces 50% of maximal effect on the bispectral index scale score; $E_0$ = baseline bispectral index scale score; $\gamma$ = measure of curve steepness; $k_{e0}$ = elimination constant from the effect-site compartment.

of the concentration-effect relationship, as characterized by the pharmacodynamic model, are presented by group in figure 4.

The BIS *versus* time data from both the combined shock-resuscitation and control groups was used to construct a population inhibitory effect sigmoid model (simple model). Scaling the $C_{50}$ by group assignment significantly improved the performance of the population pharmacodynamic model (table 4). Scaling the other pharmacodynamic parameters to group assignment did not improve the population model performance.

*Computer Simulations*

Simulations using combined pharmacokinetic/pharmacodynamic models for each study group revealed differences in the clinical pharmacology of propofol between bled-resuscitated and unbled swine. The simulation of a propofol bolus (4 mg/kg) and of a propofol infusion (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) maintained for 60 min for both study groups are presented in figure 5. The simulations

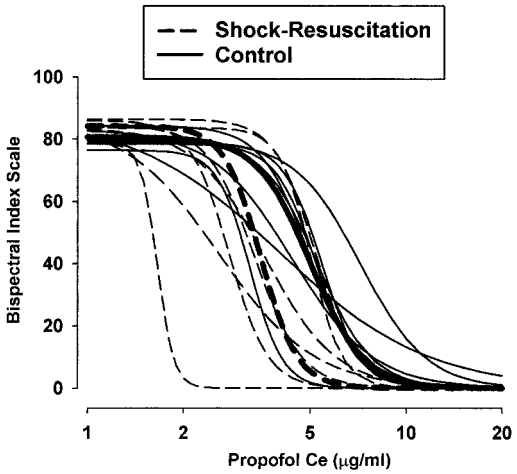


**Fig. 4. The concentration-effect relationship for each animal as characterized by the pharmacodynamic model. The solid lines represent control animals over a propofol plasma concentration range of 1 to 20 $\mu$g/ml. The dashed lines represent shock-resuscitation animals over the same range. The bold lines portray the mean pharmacodynamic model for each group. The horizontal axis is on the log scale.**

of the bolus dose yielded peak effect-site propofol concentrations of 6.8 and 5.0 $\mu$g/ml for the shock-resuscitation and control groups, respectively. To put these peak effect-site values into pharmacodynamic perspective, the $C_{50}$ and the estimated BIS score for the shock-resuscitation and control groups have been added to the plots in figure 5. In unbled (control) swine, the propofol bolus yielded a peak effect-site concentration that briefly approximated the control $C_{50}$. The BIS dropped to 40 at the peak effect-site concentration and then returned to baseline over the next 10 min. By contrast, simulation of the same bolus administered to bled swine generated a peak effect-site concentration that exceeds the shock-resuscitation $C_{50}$ for 10 min. The BIS dropped precipitously to less than 10 shortly after administration of propofol and returned to baseline 15 min after the bolus (fig. 5, A).

The simulation of the 60-min infusion yielded steady state effect-site propofol concentrations of 5.1 and 4.6 $\mu$g/ml for the control and shock-resuscitation groups, respectively (fig. 5, B). In simulations of unbled swine, the infusion required 60 min to reach the control $C_{50}$. The BIS reached 40 near the end of the 1-h infusion. With the same dose administered to simulations of bled then resuscitated swine, the shock-resuscitation $C_{50}$ was attained within 17 min and persisted above the shock $C_{50}$ for 5 min after termination of the infusion (a total of 48 min above the $C_{50}$). The BIS dropped to less than 40 when the effect-site concentration exceeded the $C_{50}$ (17 min into the infusion) and reached a minimum of 4 at the end of the 60-min infusion.

In the second set of simulations, a target-controlled infusion designed to maintain the effect-site concentration at the $C_{50}$ for 60 min was simulated for each group. The amount of propofol required was 14.8 mg/kg to 11.0 mg/kg for the control and shock-resuscitation models. respectively.

## Discussion

Our hypotheses that severe blood loss followed by moderate crystalloid resuscitation would not influence the pharmacokinetics but would alter the pharmacodynamics of propofol were confirmed. We previously reported that propofol administered in the presence of moderate hemorrhage (30 ml/kg) led to significantly altered pharmacokinetics and an increase in the potency of propofol.[2] By comparison to our previous work, the essential findings of this study were twofold: crystalloid resuscitation after severe blood loss nearly reversed the alterations in propofol pharmacokinetics previously observed in moderate hemorrhagic shock and partially reversed the changes in propofol pharmacodynamics observed in moderate hemorrhagic shock. The clinical relevance of these findings is that in patients who suffer

**Table 4. Simple and Covariate Expanded Combined Population Models**

| Parameter Estimates | Simple Population Model | Scaled Population Model |
|---|---|---|
| $E_0$ | 82 (1.5%) | 82 (1.0%) |
| $\gamma$ | 3.5 (10.0) | 3.7 (9.1) |
| $C_{50}$ | 2.9 (16.1%) | 2.4 + [FLAG*2.7] (10.0%, 13.9%) |
| $k_{eo}$ | 0.12 (4.9%) | 0.11 (5.2%) |
| Objective Function | 2144 | 2088 |

Values in parentheses are the coefficient of variation. The $C_{50}$ parameter in the scaled model has two coefficients of variation for each of the two fixed effects: the $C_{50}$ and the delta $C_{50}$ based on group assignment. The objective function is $-2 \times$ log likelihood.

$C_{50}$ = effect site concentration that produces 50% maximal effect on the bispectral index scale; $E_0$ = baseline bispectral index scale; $\gamma$ = measure of curve steepness; $k_{eo}$ = elimination constant from the effect-site compartment.

from hemorrhagic shock, typically some degree of resuscitation has been undertaken before the administration of an intravenous anesthetic such as propofol. Thus, the potentially worrisome consequences of pronounced and prolonged drug effect from propofol during hemorrhagic hypotension are in some measure diminished with restoration of intravascular volume.

### *Influence of Hemorrhagic Shock-Resuscitation and Propofol on Cardiovascular Performance*

The hemorrhage protocol produced an estimated 60% decrease in blood volume assuming a vascular volume of 70 ml/kg for swine, resulting in severe hemorrhagic shock.[15] An important feature of the hemorrhagic shock model was that all of the bled animals were resuscitated after the onset of cardiovascular decompensation. This was defined as the point during isobaric hemorrhage at which blood had to be reinfused to maintain the target MABP (40 mm Hg). This ensured a consistent degree of cardiovascular compromise before resuscitation. The resuscitation protocol replaced approximately 140% of the shed blood volume with lactated Ringer's solution to maintain a near normotensive MABP. This resuscitative effort most likely represents incomplete volume replacement. The resuscitative effort partially restored hemodynamic function as manifest by a return of central venous pressure and cardiac index to baseline values and a partial decrease in the shock-induced tachycardia. Resuscitation with crystalloid, however, did not restore metabolic homeostasis, as manifest by a persistent lactic acidemia and base deficit.

Under these hemodynamic and metabolic conditions and appreciating the previously reported hemodynamic effects of propofol,[2,16,17] we investigated whether a brief high-dose infusion would impact cardiovascular function differently in bled resuscitated swine than in unbled controls. We found the cardiovascular response to propofol exaggerated in the bled-resuscitated group. For example, during the propofol infusion, the cardiac index

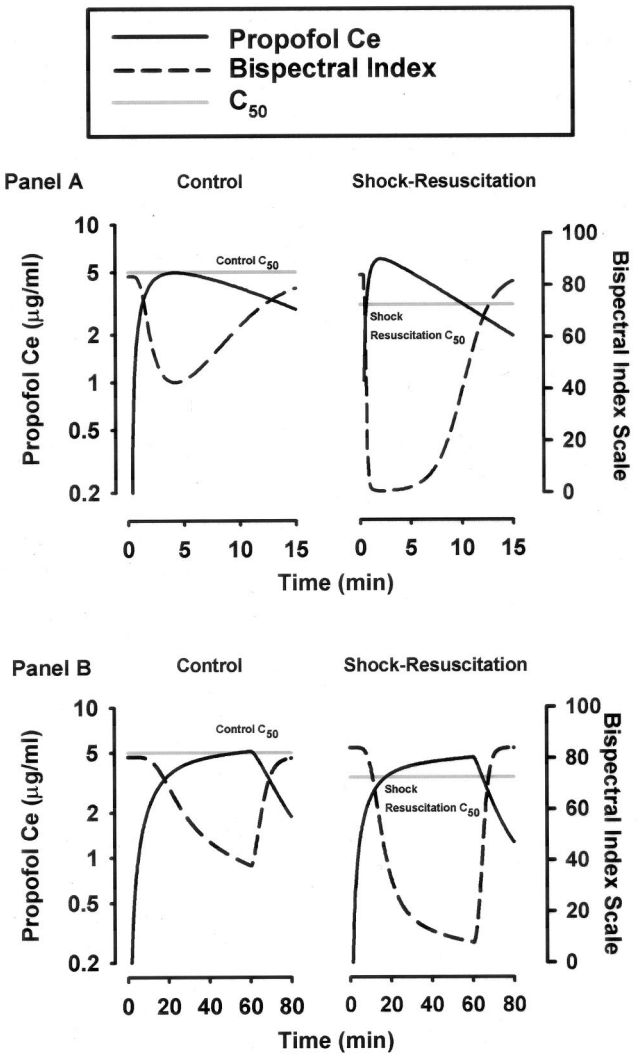


**Fig. 5. Simulation of the effect-site propofol concentration that results from 4 mg/kg bolus (*A*) and from 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion for 60 min (*B*). The plots on the left represent the propofol effect-site concentration (*solid black line*), the bispectral index scale (*dashed black line*), and the effect-site concentration that produces 50% of the maximal effect in the bispectral index scale (*gray line*) estimated from the control group pharmacokinetic and pharmacodynamic models. The plots on the right represent the same parameters estimated from the shock-resuscitation group pharmacokinetic and pharmacodynamic models.**

dropped 1.7 $l \cdot min^{-1} \cdot m^{2-1}$ in the shock-resuscitation group but only dropped 0.2 $l \cdot min^{-1} \cdot m^{2-1}$ in the control group. The hemodynamic changes observed in the control group were consistent with what other authors have reported as the hemodynamic consequences of bolus dose and continuous infusion of propofol in canine and swine models.[18–21] The large hemodynamic changes in the shock-resuscitation group illustrate how severe blood loss followed by partial resuscitation can lead to potentially large cardiovascular changes with the administration of propofol. In fact, a significant clinical correlate from this analysis is that despite a near-normal hemodynamic profile after partial resuscitation for se-

**Table 5. Comparison of Shed Blood Volume, Resuscitation Volume, Propofol Dose, and Peak Plasma Propofol Concentration Between Hemorrhage Only and Hemorrhage-Resuscitation Studies**

| | Hemorrhage Only | | Hemorrhage-Resuscitation | |
|---|---|---|---|---|
| | Control Group | Bled Group | Control Group | Bled-Resuscitated Group |
| Shed Blood Volume (ml/kg) | 0 | 30 | 0 | 42 ± 2 |
| Resuscitation Volume (ml/kg) | 0 | 0 | 0 | 59 ± 6 |
| Propofol Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) | 200 | 200 | 750 | 750 |
| Peak Plasma Propofol Concentration ($\mu g/ml$) | 1.3 ± 0.1 | 3.2 ± 0.5 | 16.6 ± 1.8 | 18.1 ± 3.0 |
| Cardiac Index Prior to the Propofol Infusion ($L \cdot min^{-1} \cdot m^{-2}$) | 5.0 ± 0.5 | 2.6 ± 0.1 | 4.8 ± 0.2 | 5.0 ± 0.5 |

vere blood loss, resuscitation should continue to minimize the potentially severe hemodynamic depression that can be associated with the administration of propofol.

### *The Influence of Hemorrhagic Shock and Resuscitation on Propofol Pharmacokinetics*

Based on the premise that resuscitation after hemorrhagic shock would restore cardiac output and systemic blood flow, we anticipated propofol plasma concentrations would be similar between the shock-resuscitation and control groups. Inspection of the raw data revealed very similar plasma concentrations over time between groups and suggested minimal pharmacokinetic differences between groups. In fact, the 95% confidence interval in the mean difference of the peak plasma propofol concentrations between groups was relatively wide but did include 0, suggesting that the groups were similar and if a difference between groups indeed existed, it could be in either direction (*i.e.*, the control group has a higher peak plasma concentrations than the shock-resuscitation group or *vice versa*).

Comparison of individual pharmacokinetic parameters by group corroborated this prediction but did reveal some subtle differences between groups, although the differences were not significant (table 2). It is important to recognize that the three-compartment model representation used to describe the propofol pharmacokinetics is an illustration of a triexponential equation and that the volumes and clearances have no real physiologic or anatomic correlate. However, the central compartment volume tended to be smaller in the hemorrhage-resuscitation group. Although not significant, this finding suggested that the vascular volume, as anticipated, would be depleted in comparison to the control group. By contrast, the slow equilibrating peripheral compartment (V3) tended to be larger in the hemorrhage-resuscitation group, but the difference was not significant. A potential explanation for this subtle increase may be that the distribution of propofol is related to the altered organ blood flow with resuscitation after hemorrhage.[22,23] Although we did not measure blood flow in specific vascular beds during and after hemorrhage and resuscitation, we did observe a drop in the systemic vascular resistance with resuscitation, suggesting that the distribution of blood flow may have been altered before the propofol infusion. Nevertheless, the impact of these presumed changes in the distribution of blood flow on propofol pharmacokinetics appears to be minimal.

To further explore potential differences between groups, a mixed effects population model was built to examine how covariates of interest might improve model performance. The noncovariate-adjusted mixed effects population model (simple model) performed well. The introduction of group assignment, shed blood volume, resuscitation volume, or cardiac index did not statistically improve the minimization objective function or model performance. Our interpretation of this pharmacokinetic analysis was that severe hemorrhage followed by resuscitation did not significantly alter the pharmacokinetics of propofol.

These findings are in stark contrast to what we previously reported in bled, unresuscitated swine that were administered propofol, fentanyl, or remifentanil.[2,12,24] In these studies, hemorrhagic shock alone significantly altered the pharmacokinetic profile of each of these intravenous anesthetics, leading to large increases in the plasma concentrations when compared to equivalent doses administered to unbled swine. The changes in drug clearance and distribution were thought to be primarily a function of decreased cardiac output and tissue perfusion. For propofol, we previously reported a large decrease in clearance from the rapid and slow equilibrating peripheral compartments as a consequence of moderate hemorrhage (30 ml/kg) and a 48% decrease in the cardiac index. As Upton *et al.* have described, cardiac output plays a critical role in determining the pharmacokinetics of propofol.[5] This current study illustrates the significant role cardiac output can have on manipulating propofol pharmacokinetics.

In comparison to our previous work evaluating the impact of blood loss alone on the pharmacologic behavior of propofol,[2] there are a few subtle differences in this current study that merit discussion. First, the propofol dose is over threefold higher in this current study than in our previous work (table 5). The reason we used a continuous propofol infusion of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min in our previous work (hemorrhage only) was

that through a series of pilot studies, we discovered that bled animals would not tolerate a higher infusion rates and would not survive the 3-h segment of the study protocol dedicated to collecting propofol plasma concentrations. Second, in our previous study, we found the hemorrhage model (without resuscitation) utilized in this current study to be too severe. To get animals to survive the hemorrhage-only protocol that we had successfully used for remifentanil,[12] the target MABP was increased from 40 to 50 mm Hg and the isobaric hemorrhage terminated after removing only 30 ml/kg. By contrast, in this current study, animals tolerated a more severe hemorrhage model (target blood pressure of 40 mm Hg until 42 ml/kg had been removed) and the administration of a larger 10 min propofol infusion ($750\ \mu g \cdot kg^{-1} \cdot min^{-1}$). This comparison illustrates that although the resuscitative effort only partially restored intravascular volume and that the lactated Ringer's solution most likely distributed out of the vascular compartment into extravascular tissues, the resuscitative effort significantly improved the ability of the animals to tolerate the cardiovascular-depressant effects of propofol. Had there been no resuscitation, as we observed in our previous work with propofol using a hemorrhage-only protocol, we anticipate that all of the animals would have expired with the severity of the hemorrhagic shock implemented in this current study.

### *Influence of Hemorrhage and Resuscitation on Propofol Pharmacodynamics*

We used the BIS as a surrogate measure of propofol effect and found that a 10 min continuous infusion of propofol produced a more pronounced decrease in the BIS in the shock-resuscitation group than in the control group. Potential sources for this difference could be either changes in pharmacokinetics or pharmacodynamics. We reported minimal differences, if any, in the pharmacokinetic analysis between groups. The more likely explanation of these differences is a change in the pharmacodynamics. The pharmacodynamic analysis corroborated this assessment.

Previous work by both DePaepe *et al.* and our laboratory have reported an increase in propofol potency after moderate hemorrhagic shock in rodents and swine.[1,2] Although metrics used to describe drug effect were somewhat different, in both studies, investigators reported a reduction in the $C_{50}$ for propofol. For example DePaepe *et al.* reported a 23% reduction in the effect-site concentration at the return of the righting reflex in rodents after a 20 ml/kg hemorrhage. Similarly, we reported a 2.7-fold decrease in the effect-site concentration required to achieve 50% of the maximal effect in the BIS after a 30 ml/kg hemorrhage. A proposed explanation for the observed increased in propofol potency is that hemorrhagic shock leads to an increase in circulating beta endorphins[25–27] that act synergistically with propofol, as has been previously reported with other opioids.[28,29] Recent work by DePaepe *et al.,* however, has revealed that endorphin antagonism with naloxone does not influence end-organ sensitivity to propofol during hemorrhagic shock in the rat.[30]

Other potential sources of increased end-organ sensitivity to propofol include the release of unspecified substances that act synergistically with propofol, an alteration in the end-organ response to propofol as a consequence of the lactic acidemia, hyperkalemia, tissue hypoxia or other metabolic disturbance associated with severe hemorrhagic shock, and an undetected increase in the fraction of unbound propofol as a consequence of decreased lipophilic binding sites within whole blood[31] as a consequence of resuscitation from hemorrhagic shock.

In this current study, we explored whether the increase in end-organ sensitivity to propofol observed after hemorrhagic shock would persist after resuscitation. We reported an increase in propofol potency, but when compared with our previous work, the increase was reduced with resuscitation (from a 2.7-fold to a 1.5-fold decrease in the $C_{50}$). Although the mechanism for this phenomenon is not well understood, increased end-organ sensitivity associated with severe blood loss persisted after resuscitation despite near normalization of the pharmacokinetics. A limitation of this analysis is that the time course of the observed changes in pharmacodynamics was not studied. It is probable that over time, the pharmacodynamics would eventually return to baseline.

### *Computer Simulations*

In previous work DePaepe *et al.* reported a 2.5-fold reduction in dose *via* continuous infusion to achieve the same drug effect from propofol after a 20 ml/kg blood loss.[1] Similarly, we reported a 5.4-fold reduction in the dose of propofol required to reach a target effect-site concentration after a 30 ml/kg blood loss.[2] To assess how resuscitation might reverse these large changes in propofol dosing requirements after hemorrhagic shock, we explored the results of this current study through a series of simulations using combined pharmacokinetic/pharmacodynamic models for each study group (shock-resuscitation and control). In the first set of simulations, both the bolus dose and continuous infusion of propofol were designed to achieve the $C_{50}$ for propofol in the control group. The effect-site concentration in simulations using shock-resuscitation pharmacokinetic and pharmacodynamic parameter estimates exceeded the $C_{50}$ for the shock-resuscitation group, demonstrating a more rapid onset and prolonged effect. This is perhaps best illustrated by observing the change in the BIS over time where the drop in the BIS was more precipitous, lower, and of longer duration in the simulations using the shock-resuscitation pharmacokinetic and pharmacodynamic models than those simulations using the control models. The extent and duration of the overshoot, how-

ever, was markedly reduced when compared with our previous work with propofol after hemorrhagic shock alone, illustrating the overall restorative impact of resuscitation on the pharmacologic behavior of propofol. In the second set of simulations, we demonstrated a 1.5-fold decrease in the amount of propofol required to achieve an equivalent effect between bled-resuscitated and unbled swine. This is in contrast to the large decrease (over fivefold) we previously reported after moderate hemorrhage alone.

*Study Limitations*

There are several limitations to this line of investigation that have been discussed in previous work.[1,2,12,24,32] Some of these include pharmacokinetic and pharmacodynamic analysis in the presence of isoflurane and trace amounts of induction agents, BIS as a surrogate of drug effect in swine, differences among species in their response to hemorrhagic shock in terms of their splenic reserve and dissimilar hemoglobin oxygen p50 values, and (intravenous) differences in species with regard to the dosing required to achieve a desired clinical effect.

An additional limitation of this study is that the resuscitation protocol used does not reflect clinical practice. Resuscitation from severe hemorrhagic shock is rarely done with crystalloid alone. Current guidelines from the American College of Surgeons, Committee on Trauma recommend a preliminary bolus of 20 ml/kg of crystalloid and, if restoration of intravascular volume remains inadequate, continued resuscitation with packed erythrocytes[15] (we administered 59 ml/kg of crystalloid). It is not clear how resuscitation with blood products or colloids would have influenced the results of the current pharmacokinetic and pharmacodynamic analysis, but we anticipate that restoration of the vascular volume would have been more complete and the adverse cardiovascular response to propofol in the bled-resuscitated animals would have been reduced.

Another limitation of the study is that at the time propofol was administered, the resuscitation infusion pump was turned off. During and after the propofol infusion, there were more pronounced hemodynamic changes in the hemorrhage-resuscitation group than in the control group. At this point, there were two conflicting goals in our experimental design: maintain the lactated Ringer's infusion to ensure consistency in the hemodynamic state throughout the study protocol *versus* minimize the impact of large volumes of resuscitation fluid on determining propofol pharmacokinetics. We chose to minimize the impact of resuscitation on our pharmacokinetic characterization of propofol. In doing so, we gave up some of the control required to ensure that all animals maintained an equivalent degree of metabolic compromise throughout the propofol assay collection period. This may contribute to additional inter-subject variability in the hemorrhage-resuscitation group and make detecting differences between groups difficult. Furthermore, as a crystalloid, lactated Ringer's solution will distribute over time from the vascular compartment into the extravascular space. Once the lactated Ringer's infusion was stopped, its contribution to restoring intravascular volume most likely diminished over the 3-h study period. This phenomenon may add an additional source of variability to the propofol pharmacokinetic analysis in the hemorrhage-resuscitation group.

An additional limitation to this work is in accounting for changes in the amount of free propofol between groups. Propofol is 96–98% protein bound.[33] DePaepe *et al.* explored the changes in unbound propofol between bled and unbled rodents and found no differences in free fractions of propofol between groups.[1] In the current study, plasma protein content and the amount of unbound propofol were not measured and compared between groups. It is plausible that with a large volume of crystalloid resuscitation (*e.g.*, 59 ml/kg in 60 min), plasma protein content may have changed significantly. Furthermore, the metabolic disturbance observed in our hemorrhage-resuscitation model might have influenced the amount of unbound propofol available to exert a pharmacologic effect. Significant differences in the amount of unbound propofol may, in fact, serve as an explanation for the apparent increase in end-organ sensitivity to propofol observed in the hemorrhage-resuscitation group.

In summary, we studied the influence of severe hemorrhage followed by resuscitation with lactated Ringer's solution on the pharmacologic behavior of propofol. Perhaps the most interesting finding of this study was that partial resuscitation nearly eliminated the pharmacokinetic changes and attenuated the pharmacodynamic changes associated with hemorrhagic shock. This restorative impact of partial resuscitation on propofol pharmacokinetics and pharmacodynamics is even more impressive given that the hemorrhage model used in this study was significantly more severe (42 ml/kg bleed) than our previous work (30 ml/kg bleed with no resuscitation) in which the blood loss significantly altered the pharmacologic behavior of propofol. Nevertheless, these results demonstrated that despite resuscitation, a modest reduction in dose might be prudent to avoid unwanted cardiovascular depression and potentially prolonged effect in the setting of resuscitation after hemorrhagic shock.

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