

# Influence of Cardiac Output on Plasma Propofol Concentrations during Constant Infusion in Swine

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**Background:** As propofol is a high-clearance drug, plasma propofol concentrations can be influenced by cardiac output (CO), which can easily change in response to several factors. If propofol is metabolized in the lungs, the difference between pulmonary and arterial propofol concentrations might also be affected by CO. The objective of the current study was to assess how much plasma propofol concentrations are affected by CO and to determine how much the lungs take part in propofol elimination and in concentration changes affected by CO in anesthetized swine.

**Methods:** Thirteen swine were studied. Propofol was administered *via* a peripheral vein at a rate of  $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , and blood samples were simultaneously collected from pulmonary and femoral arteries at 0, 2, 3.5, 5, 7, 10, 20, and 30 min and at 20-min intervals up to 270 min. After 90 min of sampling (baseline 1), CO increased in response to a continuous infusion of dobutamine ( $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; high-CO state); the infusion was then stopped, and CO was allowed to return to baseline (baseline 2). Finally, CO decreased with the administration of propranolol (2.0–4.0 mg administered intravenously; low-CO state). Each hemodynamic status was maintained for 1 h.

**Results:** As CO increased 36% from baseline 1, plasma propofol concentrations decreased by 18% from baseline 1, and as CO decreased 42% from baseline 1, plasma propofol concentrations increased by 70% from baseline 1. Plasma propofol concentrations can be expressed by the following equation: plasma propofol concentration (micrograms per milliliter) =  $6.51/\text{CO} (\text{l}/\text{min}) + 1.11$  ( $r = 0.78, P < 0.0001$ ). No significant differences were observed between plasma propofol concentrations in pulmonary and femoral arteries in any state, and CO caused no apparent differences between pulmonary and arterial propofol concentrations.

**Conclusions:** An inverse relation was observed between CO and propofol concentrations. The lungs appear to have a minor effect on plasma propofol concentrations during constant infusion in anesthetized swine.

AFTER an intravenous bolus injection of propofol, the initial drug effects are likely to have a strong dependence on cardiac output (CO), which is the major determinant of the initial distribution.<sup>1</sup> Because propofol is a high-clearance drug, plasma propofol concentrations during constant infusion might be influenced by CO, which can easily change in response to surgical stimulation or administration of inotropic agents. Although Myburgh *et al.*<sup>2</sup> recently reported that exogenous catecholamine infusions decrease propofol concentrations during contin-

uous propofol infusion in an ovine model, there have been few studies comparing plasma propofol concentrations during constant infusion between hyperdynamic and hypodynamic states.

Extrahepatic clearance of propofol has been suggested, as systemic propofol clearance exceeds hepatic blood flow.<sup>3-7</sup> The lungs have been suggested as a possible site contributing to the extrahepatic clearance of propofol, although even recent reports regarding the behavior of propofol in lungs are contradictory.<sup>8,9</sup> The first-pass uptake and extraction reflect the volume of distribution of propofol in the lungs, and this uptake and extraction would not be responsible for the difference between pulmonary and arterial propofol concentrations during constant infusion. Although any metabolism of propofol in the lungs would contribute to its first-pass extraction, it would also be evident as the difference between pulmonary and arterial propofol concentrations in the steady state. If the lungs are responsible for propofol metabolism, the contribution of the lungs to the extraction of propofol might be related to CO, as the lungs are recipients of the total CO flow. The first objective of the current study was to assess how much systemic plasma propofol concentrations are affected by CO, and the second was to investigate whether the contribution of the lungs to propofol extraction is related to CO based on measurements of the difference between pulmonary and arterial propofol concentrations at various COs during controlled high or low CO conditions in anesthetized swine.

## Materials and Methods

This study was approved by the Institutional Ethics Committee (Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan). Thirteen swine were studied (body weight range, 24.0–35.0 kg; mean  $\pm$  SD,  $28.2 \pm 3.3$  kg). General anesthesia was induced by the inhalation of isoflurane (5%) in 5 l/min oxygen using a standard animal mask. After tracheostomy, anesthesia was maintained with 2% end-tidal isoflurane and an oxygen-air mixture (fraction of inspired oxygen = 0.6) *via* mechanical ventilation. A peripheral venous catheter (20 gauge) was placed in the right dorsal ear vein, and an infusion of lactated Ringer solution was maintained at a rate of  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Another peripheral venous catheter (20 gauge) was placed in the left dorsal ear vein and was used solely for propofol infusion. End-tidal carbon dioxide was maintained between 35 and 40 mmHg. Lead II of an electrocardiogram was monitored with subcutaneous elec-

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trodes introduced into the legs. A pulmonary artery catheter (5 French, 4 lumen; Nihon Kohden, Tokyo, Japan) was inserted *via* the right jugular vein, and a catheter (18 gauge) was placed in the right femoral artery. The blood temperature of the swine was maintained with heating lamps between 38.0 and 39.0°C.

Propofol was administered with an infusion pump (TE-312; Terumo, Tokyo, Japan) *via* an intravenous catheter placed in the left dorsal ear vein at a rate of  $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Blood samples were simultaneously collected from pulmonary and femoral arteries at 0, 2, 3.5, 5, 7, 10, 20, and 30 min and at 20-min intervals up to 270 min. Blood-plasma samples were immediately separated and stored at 5°C on ice until extraction and assay. Within 12 h of sampling, plasma propofol concentrations were determined using high-performance liquid chromatography with fluorescence detection at 310 nm after excitation at 276 nm (CTO-10A, RF550, and C-R7A; Shimadzu, Kyoto, Japan).<sup>10</sup> For each batch of blood samples, a standard curve was computed by adding pure propofol liquid to drug-free pig plasma to achieve concentrations of 1.0, 5.0, 10.0, and 15.0  $\mu\text{g}/\text{ml}$ . Linear regression (least-squares method) was conducted using plasma propofol concentrations as the dependent variable. Propofol concentrations in this study were calculated using the obtained regression equation. The lower limit of detection was 15 ng/ml, and the mean intraassay coefficient of variation was 7.4%. The pulmonary extraction ratio was calculated as follows:

$$100 \times (\text{plasma propofol concentration in pulmonary artery} - \text{plasma propofol concentration in femoral artery}) / \text{plasma propofol concentration in pulmonary artery} (\%)$$

Cardiac output values were measured by the thermodilution method before propofol administration and at each blood sampling time after 50 min up to 270 min. After 90 min of blood sampling (baseline 1 = 50, 70, and 90 min), CO was increased with a continuous infusion of dobutamine at a rate of  $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  until 150 min of blood sampling (high-CO state = 110, 130, and 150 min), after which continuous infusion of dobutamine was stopped and CO returned to baseline until 210 min of blood sampling (baseline 2 = 170, 190, and 210 min). Finally, CO was decreased with the administration of 2.0–4.0 mg propranolol (low-CO state = 230, 250, and 270 min). After hemodynamic stability was achieved and maintained for at least 10 min, CO was determined with a thermodilution computer (Cardiac Output Computer, MTC6210; Nihon Kohden, Tokyo, Japan) using 5 ml of cold 5% glucose injected into the right atrium. The indicator for thermodilution was administered by the same person during apnea at the end

of expiration. Each CO was measured four times, and the mean of the last three values was recorded.

Estimates of indocyanine green (ICG) clearance were made for each hemodynamic status at 70, 130, 190, and 250 min after propofol infusion. ICG clearance was estimated after a single bolus dose of 5 mg administered intravenously during the last 15 min according to Caesar *et al.*<sup>11</sup> Concentrations of ICG in the plasma at 5, 10, and 15 min were measured by spectrophotometry at 805 nm. ICG plasma concentrations were converted to blood concentrations by multiplying them by  $(1 - \text{hematocrit}/100)$ , as ICG is distributed only in the plasma fraction of blood. Because ICG concentrations decrease monoexponentially, dye concentrations at time  $t = 0$  ( $C_{t0}$ ) can be extrapolated by extending the slope of the dye dilution curve transcribed to a semilogarithmic graph. Blood volume was calculated using the following formula: blood volume =  $I/C_{t0}$ , where  $I$  is the amount of ICG (5 mg) injected. The ICG clearance slope ( $K$ ) was calculated *via* linear regression of the semilogarithmic graph, and liver blood flow was also calculated using the following formula: liver blood flow =  $K \times$  blood volume.

#### Statistical Analysis

Data are expressed as mean values  $\pm$  SD. Heart rates, mean arterial pressures, COs, propofol concentrations, pulmonary extraction ratio, blood volumes, and liver blood flows for each hemodynamic state were analyzed by repeated-measures one-way analysis of variance. If the analysis of variance was found to be significant, the Scheffé F test was performed to compare the difference in values between each condition. Differences in propofol concentrations between pulmonary and femoral arteries at each time point were evaluated using the student  $t$  test for dependent samples. Differences in propofol concentrations between pulmonary and femoral arteries for each hemodynamic state were analyzed with repeated-measures analysis of variance. As recommended by Upton *et al.*<sup>1</sup> and Myburgh *et al.*,<sup>2</sup> plasma propofol concentrations were plotted against the inverse of CO values, and the linear regression equations were calculated by simple linear regression analysis.  $P < 0.05$  was considered statistically significant.

## Results

Figure 1 shows the relation between the time course of the experiment and plasma propofol concentrations in the femoral artery or the change in CO during constant infusion at  $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  in all animals. Plasma concentrations of propofol increased after the start of constant infusion and reached a pseudosteady state at 50 min. There was a clear tendency toward decreases in concentration values with increasing CO, and increases with decreasing CO. Plasma concentrations at 70 (base-

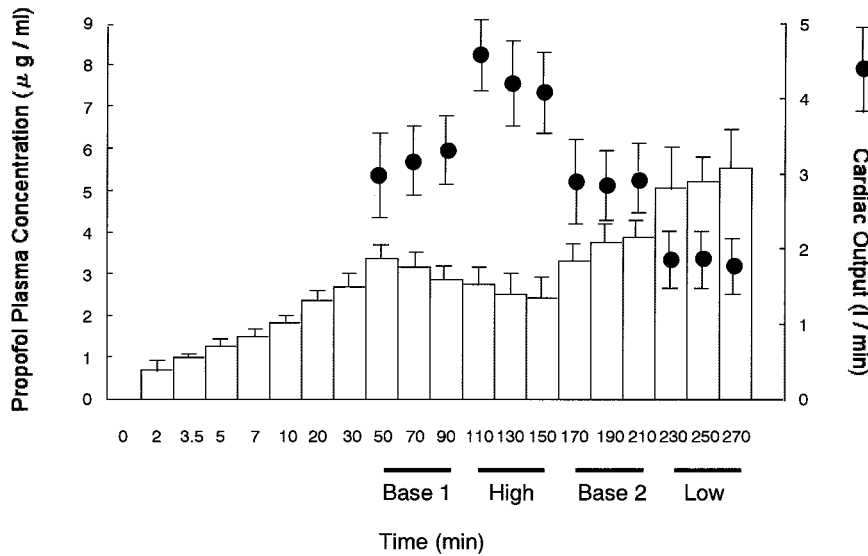


Fig. 1. The relation between the time course of the experiment and plasma propofol concentrations in the femoral artery or changes in cardiac output (CO) during constant infusion at  $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  in anesthetized swine. Circles show the CO at each time. Vertical bars represent 95% confidence intervals. Base 1 = baseline 1; High = high-CO state; Base 2 = baseline 2; Low = low-CO state.

line 1,  $\text{CO} = 3.16 \pm 0.73 \text{ l/min}$ ), 130 (high-CO state,  $\text{CO} = 4.21 \pm 0.96 \text{ l/min}$ ), 190 (baseline 2,  $\text{CO} = 2.84 \pm 0.85 \text{ l/min}$ ), and 250 (low-CO state,  $\text{CO} = 1.87 \pm 0.63 \text{ l/min}$ ) min after the start of constant infusion were  $3.17 \pm 0.54$ ,  $2.51 \pm 1.06$ ,  $3.77 \pm 0.89$ , and  $5.23 \pm 1.16 \mu\text{g/ml}$ , respectively. Figure 2 shows the relation between the time course of the experiment and the mean pulmonary extraction ratios for all animals. The extraction ratio reached a peak at 2 min ( $9.0 \pm 16.9\%$ ); however, there were no significant differences between extraction ratios at any time point. No significant differences were observed between plasma propofol concentrations in the pulmonary and femoral arteries at each time point. Heart rates, mean arterial pressures, COs, plasma propofol concentrations in both pulmonary and femoral arteries, blood volumes, and liver blood flows for each hemodynamic state are shown in table 1. Heart rate changed significantly between each hemodynamic status except between that at baseline 1 and that at the low-CO

state. Mean arterial pressure changed significantly between that at baseline 1 and that at the low-CO state, between that at baseline 2 and that at the high-CO state, and between that at the high-CO state and that at the low-CO state. CO values were also significantly changed between each hemodynamic status, except between baseline 1 and baseline 2 values. Plasma propofol concentrations in both pulmonary and femoral arteries changed significantly according to the hemodynamic state. There were significant differences between plasma concentrations for each hemodynamic state except between baseline 1 and baseline 2, and between baseline 1 and the high-CO state. There was no significant difference between plasma propofol concentrations in pulmonary and femoral arteries for any hemodynamic state. In addition, there were no statistically significant changes in blood volumes ( $P = 0.39$ ), although the liver blood flow at the low-CO state was significantly lower than that at baseline 1 and at the high-CO state. Figure 3 shows the

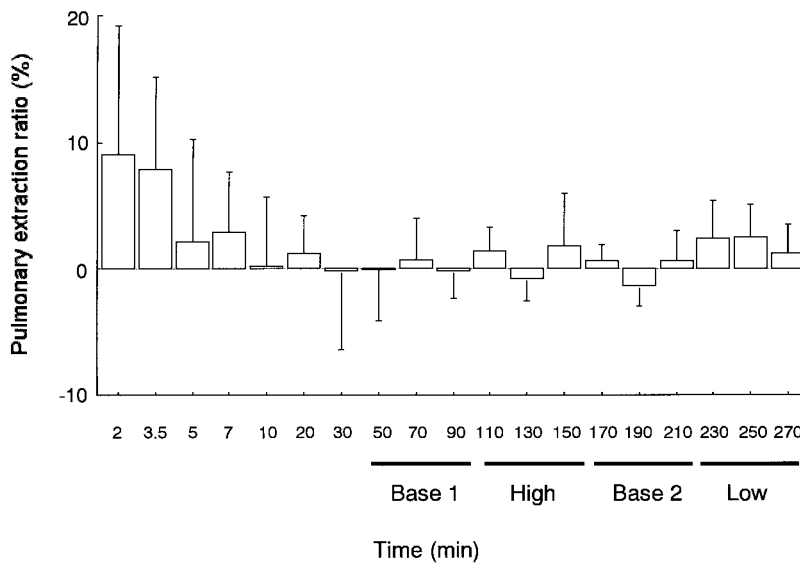


Fig. 2. The relation between the time course of the experiment and the pulmonary extraction ratio during constant infusion at  $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  in anesthetized swine. Vertical bars represent 95% confidence intervals. Base 1 = baseline 1; High = high-cardiac output (CO) state; Base 2 = baseline 2; Low = low-CO state.

**Table 1. Heart Rate, Mean Arterial Pressure, Cardiac Output (CO), Plasma Propofol Concentration in Pulmonary and Femoral Arteries, Blood Volume, and Liver Blood Flow for Each Hemodynamic State**

	Base 1	High	Base 2	Low
Heart rate (freq/min)	112.5 ± 21.4	200.2 ± 24.1*	152.5 ± 34.6*†	97.5 ± 16.2†‡
Mean arterial pressure (mmHg)	61.4 ± 10.2	74.1 ± 15.0	55.4 ± 10.6†	41.5 ± 10.8*†
Cardiac output (l/min)	3.15 ± 0.77	4.29 ± 0.90*	2.88 ± 0.86†	1.83 ± 0.64*†‡
Propofol concentration (pulmonary) (μg/ml)	3.12 ± 0.68	2.57 ± 0.96	3.65 ± 0.89†	5.40 ± 1.63*†‡
Propofol concentration (femoral) (μg/ml)	3.10 ± 0.64	2.55 ± 0.97	3.65 ± 0.89†	5.28 ± 1.54*†‡
Blood volume (l)	4.72 ± 2.02	3.19 ± 2.03	3.68 ± 2.08	3.73 ± 2.12
Liver blood flow (l/min)	0.51 ± 0.25	0.48 ± 0.36	0.33 ± 0.17	0.23 ± 0.16*†

\*  $P < 0.05$  versus baseline 1; †  $P < 0.05$  versus high CO state; ‡  $P < 0.05$  versus baseline 2.

Base 1 = baseline 1; High = high CO state; Base 2 = baseline 2; Low = low CO state; Freq = frequency.

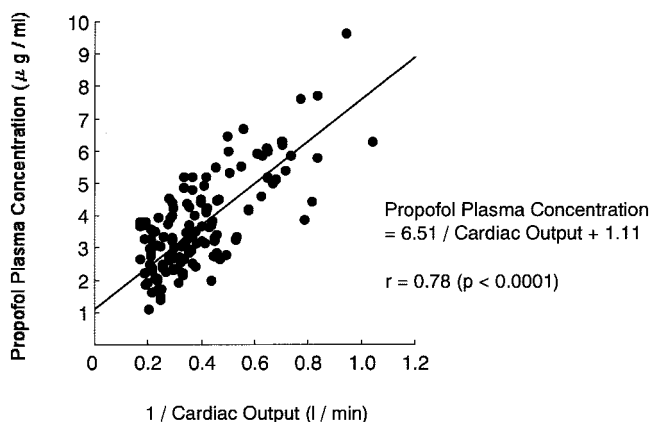
linear regression of plasma propofol concentrations in the femoral artery against the inverse of CO for all animals. Plasma propofol concentrations can be expressed by the following equation:

$$\text{plasma propofol concentration } (\mu\text{g/ml}) \\ = 6.51/\text{CO (l/min)} + 1.11 \quad (r = 0.78, p < 0.0001).$$

## Discussion

The results of the current study indicate that plasma propofol concentrations are influenced by CO during constant infusion, with concentrations decreasing or increasing with increasing or decreasing CO. As CO increased 36% from baseline 1, plasma propofol concentrations decreased by 18% from baseline 1, and as CO decreased 42% from baseline 1, plasma propofol concentrations increased by 70% from baseline 1. No apparent pulmonary extraction of propofol was observed in any state.

There was a significant correlation between plasma propofol concentrations and the inverse of CO (fig. 3). Upton *et al.*<sup>1</sup> reported an inverse relation between CO and propofol concentrations after short infusion, and Myburgh *et al.*<sup>2</sup> recently reported observing the same



**Fig. 3. Linear regression analysis of plasma propofol concentrations in the femoral artery against the inverse of cardiac output for all swine.**

relation during longer propofol infusions in their study of the high-CO state induced by catecholamine infusions in an ovine model. According to these reports, we plotted the relation between plasma propofol concentrations and the inverse of CO ( $r = 0.78$ ,  $P < 0.0001$ ) and obtained a better linear relation than between plasma propofol concentrations and CO ( $r = 0.67$ ,  $P < 0.0001$ ), not only from baseline to high CO, but also over a wide range from low ( $1.83 \pm 0.64$ ) to high CO ( $4.29 \pm 0.90$ ).

As several factors are thought to affect propofol plasma concentrations, it is difficult to describe the mechanisms of the phenomenon observed. In our study, propofol plasma concentrations decreased at high CO, despite a slight decrease in blood volume (although not statistically significant), and the minimal changes in blood volume could not account for the decreases or the increases in propofol plasma concentrations. Although liver blood flow at low CO was significantly lower than in other states, with the low CO increasing the plasma propofol concentrations by decreasing the elimination clearance, liver blood flow at high CO did not increase, and no significant changes were observed in any state other than at low CO. Furthermore, lung metabolism appeared to have almost no effect on the CO-dependent changes in propofol plasma concentrations. These results suggested that the extraction of propofol by liver and lungs cannot completely account for the mechanisms involved in CO-dependent propofol kinetics.

Because the traditional compartment models assume a linear pharmacokinetic system, they cannot accurately simulate nonlinear propofol pharmacokinetics dependent on CO. Because recirculatory pharmacokinetic models incorporate CO, in contrast to conventional pharmacokinetic models, these models are often used to describe a marked dependence of pharmacokinetics on CO.<sup>12-15</sup> Such models divide the body into pulmonary and systemic subsystems through which blood flows in a recirculatory manner at a rate given by the CO. We can use this recirculatory model to suggest two mechanisms to explain this phenomenon over a wide range of CO: (1) There is a direct indicator dilution effect between the venous injection site and arterial blood (across the pulmonary subsystem). A fixed dose added to a higher CO

(or a lower CO) results in less (or more) drug or indicator per unit blood volume, and therefore lower (or higher) concentrations. (2) higher (or lower) COs imply higher (or lower) blood flows to the organs of drug elimination and distribution in the systemic subsystem that increases (or decreases) the rate of their clearance and distribution, resulting in lower (or higher) recirculated concentrations. The first mechanism would be prominent during the initial mixing phase, but it would contribute to the rapid change in plasma propofol concentrations with altered CO shown in figure 1.

Although propofol has been shown in various studies of humans and experimental animals to exert significant and sometimes differing effects on the cardiovascular system, including decreasing systemic arterial pressure, CO, and stroke volume, as well as systemic vascular resistance,<sup>16-18</sup> there have been few investigations assessing the influence of changing CO on plasma propofol concentrations during constant infusion. In our study, CO significantly decreased from  $3.57 \pm 0.76$  l/min (before administration) to  $2.97 \pm 0.87$  l/min after 50 min of constant infusion (baseline 1). Sear *et al.*,<sup>19</sup> who administered propofol to dogs by stepwise increases in infusion rates from 200 to 500  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , reported that the relation between infusion rate and drug concentration is not linear and that blood propofol concentrations increase more than expected with increasing infusion rates because of the effects of propofol on CO and liver blood flow. Their report seems to indicate the possibility that changes in CO influence plasma propofol concentrations during constant infusion.

In the current study, no significant differences were observed between plasma propofol concentrations in pulmonary and femoral arteries before and after the pseudosteady state was reached, and these concentrations did not appear to depend on CO. Although elimination clearances (calculated by constant infusion rate divided by steady state concentration) for propofol at every state were approximately twice the estimate for liver blood flow, and the lungs would have been a major site contributing to the extrahepatic clearance of propofol, the lungs do not seem to be a major site of propofol metabolism in swine. These results are consistent with the results of a recent human study by He *et al.*<sup>8</sup> They investigated both the first-pass uptake and pulmonary extraction at a pseudosteady state and concluded that metabolism is not involved in pulmonary uptake in human lungs. However, based on the results of our study, it is difficult to conclude that propofol is not metabolized in the lungs, as the differences between plasma propofol concentrations in pulmonary and femoral arteries were minimal, and the plasma propofol concentrations were variable (according to power analyses, it will require > 2,000 cases to confirm this hypothesis). Dawidowicz *et al.*<sup>9</sup> recently reported that propofol is metabolized in human lungs based on measurements of a propofol me-

tabolite (2,6-diisopropyl-1,4-quinol). We can conclude at least that the lungs seem to be only a minor contributor to the extrahepatic metabolism of propofol in anesthetized swine, and that extraction by the lungs is extremely minimal at pseudosteady state and is not related to CO. As such, the lungs do not appear to be related to the mechanisms involved in CO-dependent propofol kinetics.

Based on their study examining the skeletal muscle kinetics of propofol in anesthetized sheep, Zheng *et al.*<sup>20</sup> reported that approximately 30–40% of propofol entering skeletal muscle does not leave the muscle within a 40-min period after a continuous 20-min infusion of propofol; therefore, it is either sequestered or metabolized.<sup>20</sup> If this same observation could be made in swine, it might be speculated that this missing propofol contributes to some sort of systemic clearance, based on a short-term kinetics study.

As a limitation of the current study, we induced the changes in CO using dobutamine and propranolol; however, we did not assess whether these drugs by themselves affect plasma concentrations of propofol. In addition, Matot *et al.*<sup>21</sup> reported that 1.5% halothane inhibits propofol uptake by the lung during a single passage through the pulmonary circulation compared with 1% halothane (no significant effect). According to this report, isoflurane (2% end tidal), which was used to maintain anesthesia in our study, might have some effect on pulmonary function.

Although further investigation in a human study is necessary, the important clinical implication of our study is that blood propofol concentrations during propofol infusion anesthesia can be affected by CO, which changes easily in response to several factors, including inadequate anesthetic depth and administration of inotropic agents or adrenergic  $\beta$  antagonists.

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