

# First-pass Lung Uptake and Pulmonary Clearance of Propofol

## Assessment with a Recirculatory Indocyanine Green Pharmacokinetic Model

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**Background:** The principal site for elimination of propofol is the liver. The clearance of propofol exceeds hepatic blood flow; therefore, extrahepatic clearance is thought to contribute to its elimination. This study examined the pulmonary kinetics of propofol using part of an indocyanine green (ICG) recirculatory model.

**Methods:** Ten sheep, immobilized in a hammock, received injections of propofol (4 mg/kg) and ICG (25 mg) via two semipermanent catheters in the right internal jugular vein. Arterial blood samples were obtained from the carotid artery. The ICG injection was given for measurement of intravascular recirculatory parameters and determination of differences in propofol and ICG concentration-time profiles. No other medication was given during the experiment, and the sheep were not intubated. The arterial concentration-time curves of ICG were analyzed with a recirculatory model. The pulmonary uptake and elimination of propofol was analyzed with the central part of that model extended with a pulmonary tissue compartment allowing elimination from that compartment.

**Results:** During the experiment, cardiac output was  $3.90 \pm 0.72$  l/min (mean  $\pm$  SD). The blood volume in heart and lungs, measured with ICG, was  $0.66 \pm 0.07$  l. A pulmonary tissue compartment of  $0.47 \pm 0.16$  l was found for propofol. The pulmonary first-pass elimination of propofol was  $1.14 \pm 0.23$  l/min. Thirty percent of the dose was eliminated during the first pass through the lungs.

**Conclusions:** Recirculatory modeling of ICG allows modeling of the first-pass pulmonary kinetics of propofol concurrently. Propofol undergoes extensive uptake and first-pass elimination in the lungs. (Key words: Intravenous anesthetics; SAAM II.)

THE liver is assumed to be the primary site for elimination of propofol from the body. However, the total-body clearance of propofol has been shown to exceed hepatic blood flow<sup>1</sup> after a bolus dose followed by an intravenous infusion. Extrahepatic elimination of propofol in humans has been demonstrated by Veroli *et al.*<sup>2</sup> during the anhepatic phase of orthotopic liver transplantation. These findings suggest that extrahepatic mechanisms contribute to the clearance of propofol from blood. It is still unknown which organs are responsible for the extrahepatic elimination, but in all likelihood, these organs receive a significant portion of the cardiac output (CO); possible candidates are the kidneys and lungs.<sup>3</sup>

Pulmonary uptake can play an important role in the initial availability of propofol. Pulmonary uptake of propofol is significant in humans.<sup>4</sup> In cats, the first-pass pulmonary uptake of propofol was 60% of the dose and was independent of mechanical ventilation but dependent on halothane administration and pretreatment with fentanyl.<sup>5</sup>

Conventional compartmental models have been used extensively for determination of the pharmacokinetics of propofol.<sup>1,6,7</sup> However, these models cannot identify pulmonary elimination or describe the extent of pulmonary uptake, both of which may affect the initial availability of propofol. In contrast, recirculatory models are capable of discriminating between the central organs (including heart and lungs) and the peripheral organs and between intravascular and extravascular pharmacokinetics.<sup>8,9</sup> In a recent study, we showed that a recirculatory model can be used to describe the pulmonary uptake of alfentanil in pigs.<sup>10</sup> Therefore, recirculatory

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models should be able to describe the pulmonary uptake of propofol and identify pulmonary clearance, if present. The objective of the present study was to describe the pulmonary uptake and pulmonary first-pass elimination of propofol in sheep using the central part of a recirculatory model for indocyanine green (ICG) extended with a pulmonary compartment.

### Materials and Methods

#### *Experimental Protocol*

The local Committee for Experiments on Animals approved the study, which included 10 female sheep that weighed approximately 50 kg and were used solely for this study. Experiments were performed in the Laboratory of Large Animals at the Leiden University Medical Center. After full recovery, the animals were returned to the farm from which they were obtained.

The sheep were instrumented during general anesthesia 1 day before the experiment. Two 8-gauge cannulae (Vygon, Ecouen, France) were introduced into the right internal jugular vein and advanced into the right atrium. These cannulae were used for central venous drug injection of ICG and propofol. A third cannula was introduced into the carotid artery, advanced into the aortic root, and used for arterial blood sampling. After completion of the experiments, the catheters were removed, again during general anesthesia, on the same day or the day after the experimental day.

On the experimental day, the sheep were immobilized in hammocks in the stable. The pharmacokinetics of ICG and propofol were studied after a bolus injection. After connecting the catheter in the aortic root to the sampling device, propofol was given simultaneously with ICG. The ICG injectate was prepared by mixing 3 ml ICG (25 mg) and autologous blood to obtain the same volume as the volume of propofol that was to be injected. One milliliter of the ICG mixture was stored for later measurement of the injectate concentration, and the remainder was placed in a 20-ml syringe. The propofol (20 mg/ml) dose used was 4 mg/kg.<sup>11</sup> The syringes used for ICG and propofol were weighed before and after injection to allow calculation of the injected volumes. Before and 10 min after drug injection, an arterial blood gas sample was taken for analysis of ventilation adequacy.

Blood samples were obtained from the aortic root. Fast sampling was accomplished with the aid of a specially constructed computer-driven syringe pump. The sampling volume was 1.5 ml, which equals the dead space of

the volumes in the catheters and the extension lines to the sampling device. Blood samples were collected in an automatically rotating fraction collector containing heparinized tubes. Sampling started at 3 s before injection of the drugs (blank sample) and continued for 10 min after ICG injection. When the time between the samples was more than 3 s, a waste sample was withdrawn in the seconds before the actual blood sample was taken. Blood samples were obtained at 3-s intervals during the first minute and at 10-s intervals during the second minute. Thereafter, samples were taken at 2.5, 3, 4, 7, and 10 min. Before the experiments, a 20-ml blood sample was drawn for construction of the calibration curves of ICG and propofol.

#### *Analytical Methods*

The concentrations of both ICG and propofol were measured on the experimental day in the Anaesthesia Research Laboratory at Leiden University Medical Center. ICG was measured spectrophotometrically at 805 nm. The limit of detection was 1  $\mu\text{g/ml}$ , and the coefficient of variation was 2.6–3.9% for the relevant range of concentration. For each experiment, a reference line was constructed from whole blank blood from the sheep and known amounts of ICG. Whole-blood concentrations of propofol were determined using high-performance liquid chromatography. Details of the analysis of propofol are described in the appendix.

#### *Data Analysis*

Blood concentrations were analyzed using a recirculatory model for ICG (fig. 1A)<sup>8</sup> and the central part of this recirculatory model for propofol (fig. 1B). In the recirculatory model, the assumption is that ICG is confined to the intravascular space and defines the intravascular kinetics of other substances injected simultaneously. Using the ICG model, CO and its distribution between the parallel central and peripheral circuits were determined. Before returning to the central circulation, the CO distributes over numerous pathways on entering the peripheral circulation. Two peripheral pathways were necessary for the modeling of ICG, one fast and one slow.<sup>12</sup>

The model was fitted to the data by fitting two Erlang functions through the ICG first-pass concentration–time data. The parameters obtained from this initial fit were then entered into the computer program (SAAM II; SAAM Institute, Seattle, WA), which performed the remainder of the fitting procedure. The shape of the first-pass concentration–time curve of ICG (*i.e.*, data before evidence of ICG recirculation as judged by examining

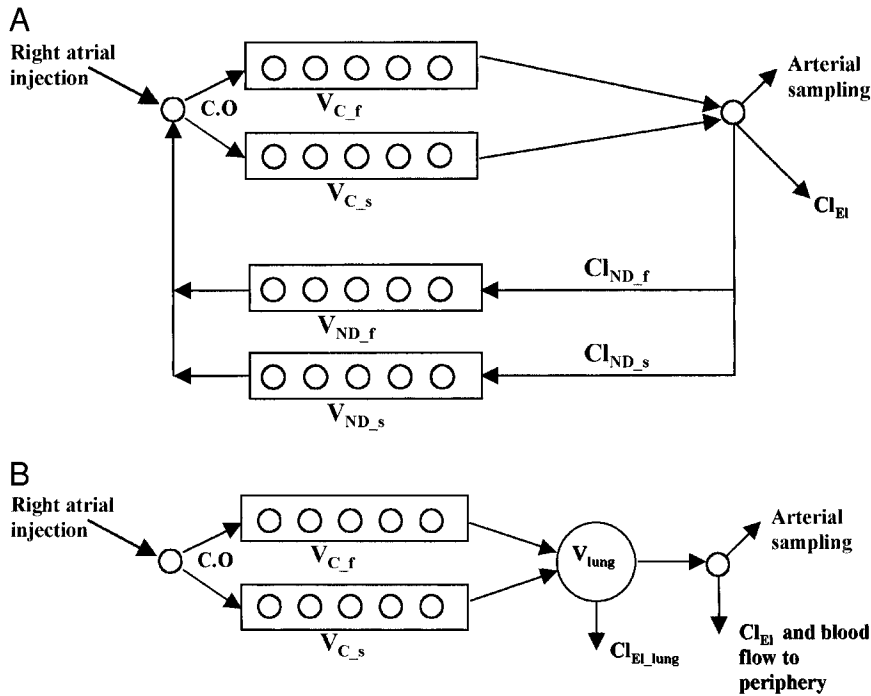


Fig. 1. (A) The recirculatory pharmacokinetic model used for analysis of the pharmacokinetics of indocyanine green (ICG). Model parameters of ICG are also used for the first-pass analysis of the simultaneously injected propofol. The intravascular compartments are represented by a rectangle with five compartments, but the actual number of compartments may vary and has no physiologic background. The intravascular model consists of a central part, receiving the full cardiac output (CO), divided into a slow ( $V_{C_s}$ ) and a fast ( $V_{C_f}$ ) central compartment, and a peripheral part, divided into a slow ( $V_{ND_s}$ ) and a fast ( $V_{ND_f}$ ) peripheral compartment and elimination clearance ( $Cl_{El}$ ). The sum of the peripheral clearances equals the CO. (B) The first-pass model for simultaneously injected propofol, which allows description of both lung uptake ( $V_{lung}$ ) and lung elimination ( $Cl_{El_{lung}}$ ).

the linear descending part of the first-pass curve when concentrations were plotted on a logarithmic scale) was described by the following equation<sup>13</sup>:

$$C(t) = A_1 \cdot \frac{k_1^{n_1} t^{n_1-1}}{(n_1-1)!} e^{-k_1 t} + A_2 \cdot \frac{k_2^{n_2} t^{n_2-1}}{(n_2-1)!} e^{-k_2 t}$$

where  $n_1$  and  $n_2$  are the numbers of compartments in series in the central delay elements;  $k_1$  and  $k_2$  are the rate constants between the compartments in series;  $n_1/k_1$  and  $n_2/k_2$  are the mean transit times of the central delay elements; and  $A_1 + A_2$  is the area under the first-pass concentration-time curve, determined by the CO and the dose of ICG. The percentage of blood flow through the fast central pathway ( $A_{C_f}$ ) equals  $[A_1/(A_1 + A_2)] \times 100$ , and the percentage of blood flow through the slow central pathway ( $A_{C_s}$ ) equals  $[A_2/(A_1 + A_2)] \times 100$ .

An Erlang function represents the convolution of  $n$  one-compartment models connected in series. The two Erlang functions were fitted to the data using the solver function in Quattro Pro (Borland, Scotts Valley, CA). The data were weighted uniformly during the first-pass fitting. The parameters obtained from the Erlang functions were used as fixed parameters in a complete recirculatory model for ICG. The model included parallel fast and slow peripheral nondistributive circuits (characterized

by  $V_{ND_f}$  and  $Cl_{ND_f}$ , and  $V_{ND_s}$  and  $Cl_{ND_s}$ , respectively) and elimination clearance ( $Cl_{El}$ ; fig. 1A). The CO of the sheep was determined by dividing the dose of ICG by the area under the first-pass concentration-time curve ( $A_1 + A_2$ ).

The model for propofol consisted of two parts: the first-pass intravascular part, which is identical to that of ICG, and a pulmonary tissue compartment. The ICG parameters for the parallel fast and slow central compartments ( $V_{C_f}$  and  $V_{C_s}$ ; together they give the central blood volume in heart and lungs [ $V_C$ ]) were used as fixed parameters in the propofol model and transported into SAAM II, which performed the fitting procedure for the pulmonary uptake and elimination (fig. 1B). The difference in first-pass concentration-time curves of ICG and propofol must be a result of pulmonary uptake or elimination. Therefore, parameters characterizing the uptake or elimination must be able to describe the difference between first-pass ICG and propofol. Only propofol data before evidence of recirculation, as judged in the same way as for ICG, were used.

#### Statistics

Differences in blood gas values were tested with a paired  $t$  test, and the criterion for rejection of the null hypotheses was  $P < 0.05$ . Data are summarized as mean  $\pm$  SD unless otherwise specified. Relationships

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**Table 1. Partial Arterial Oxygen ( $P_{aO_2}$ ) and Partial Arterial Carbon Dioxide Pressure ( $P_{aCO_2}$ ) and Hemoglobin Concentrations (Hb) in the 10 Sheep before and 10 min after Propofol Bolus Injection**

	Before Propofol	After Propofol
$P_{aO_2}$ (mmHg)	91 ± 14	79 ± 17
$P_{aCO_2}$ (mmHg)	32 ± 2	41 ± 4*
Hb (mmol/l)	5.69 ± 0.91	5.65 ± 0.85

\* Significant different from before propofol with a paired *t* test,  $P < 0.05$ .

between CO and pharmacokinetic parameters of ICG and propofol were examined with standard linear regression.

## Results

The weight of the sheep was  $47.2 \pm 1.9$  kg. All sheep became unconscious after injection of propofol, and most developed apnea for 1–3 min that required ventilation by mask; all regained consciousness within 5 min. Arterial oxygen partial pressure and hemoglobin concentrations were not significantly different before and after propofol injection. Arterial carbon dioxide partial pressure was increased after injection of propofol (table 1).

Pharmacokinetic parameters of ICG for all 10 sheep as determined with the recirculatory model are shown in table 2. By definition, the sum of flows through the nondistributive peripheral compartments and the elimination clearance of ICG equal the CO. The distribution volume at steady state ( $V_{ss}$ ),  $V_C$ , and the fast peripheral blood flow ( $Cl_{ND-f}$ ) were correlated with CO (table 2).

The concentration–time curves of ICG and propofol during the first 2 min in one sheep are shown in figure 2. First-pass fits for ICG and propofol for one sheep are shown in figure 3. The propofol data were first examined using the propofol model (fig. 1B) without the possibility of lung elimination. The only difference with the central ICG model was the lung compartment. Using

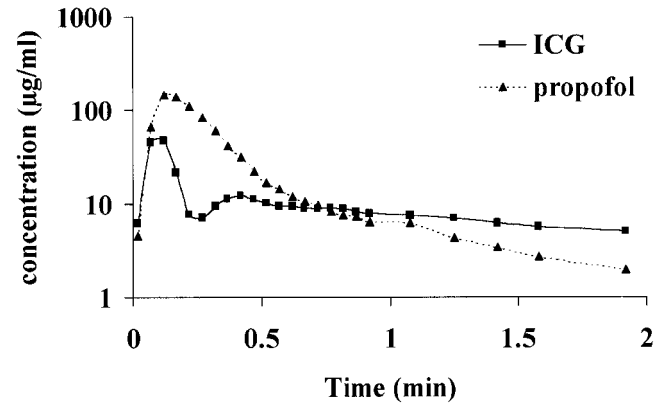
**Table 2. Parameters for the Recirculatory ICG Model for 10 Sheep during Propofol Injection**

Parameter (l/min)	Mean ± SD	Parameter (l)	Mean ± SD
CO	3.90 ± 0.72	$V_C$	0.66 ± 0.07†
$Cl_{ND-f}$	2.20 ± 0.64*	$V_{ND-f}$	0.50 ± 0.17
$Cl_{ND-s}$	0.81 ± 0.28	$V_{ND-s}$	0.80 ± 0.29
$Cl_{El}$	0.89 ± 0.27	$V_{SS}$	1.96 ± 0.44‡

\*  $Cl_{ND-f} = 0.76 CO - 0.76$ ,  $R^2 = 0.73$ ,  $P = 0.002$ .

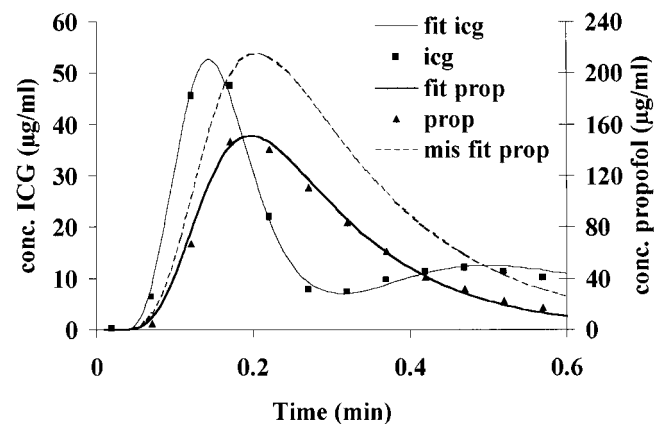
†  $V_C = 0.19 CO - 0.08$ ,  $R^2 = 0.65$ ,  $P = 0.005$ .

‡  $V_{SS} = 0.42 CO + 0.32$ ,  $R^2 = 0.48$ ,  $P = 0.026$ .



**Fig. 2. First-pass concentration–time curves of indocyanine green (ICG) and propofol in a single sheep for the first 2 min after bolus injections on a log scale (squares, measured ICG concentrations,  $\mu\text{g/ml}$ ; triangles, measured propofol concentrations,  $\mu\text{g/ml}$ ).**

this model, SAAM II was incapable of performing a good fitting procedure; all “fitted” concentrations were higher than the measured concentrations. When the possibility of lung elimination was added to the propofol model, it resulted in a good description of the measured concentrations (fig. 3). The first-pass fits of ICG and propofol for all 10 sheep are shown in figure 4. The first-pass kinetic data of propofol for the 10 sheep, as determined with the central part of the recirculatory model, are shown in table 3. CO and  $V_C$  are (by definition) the same for propofol and ICG, and the differences in the first-pass concentration–time curves of ICG and propofol are a result of pulmonary uptake and elimination. Propofol



**Fig. 3. Fits through the indocyanine green (ICG) and propofol concentration in an individual sheep obtained with a recirculatory model, showing the first 0.6 min (squares, measured ICG concentrations; thin line, fit to the ICG data; triangles, measured propofol concentrations; dashed line, “fit” to the propofol data without lung elimination; thick line, fit to the propofol data with lung elimination).**

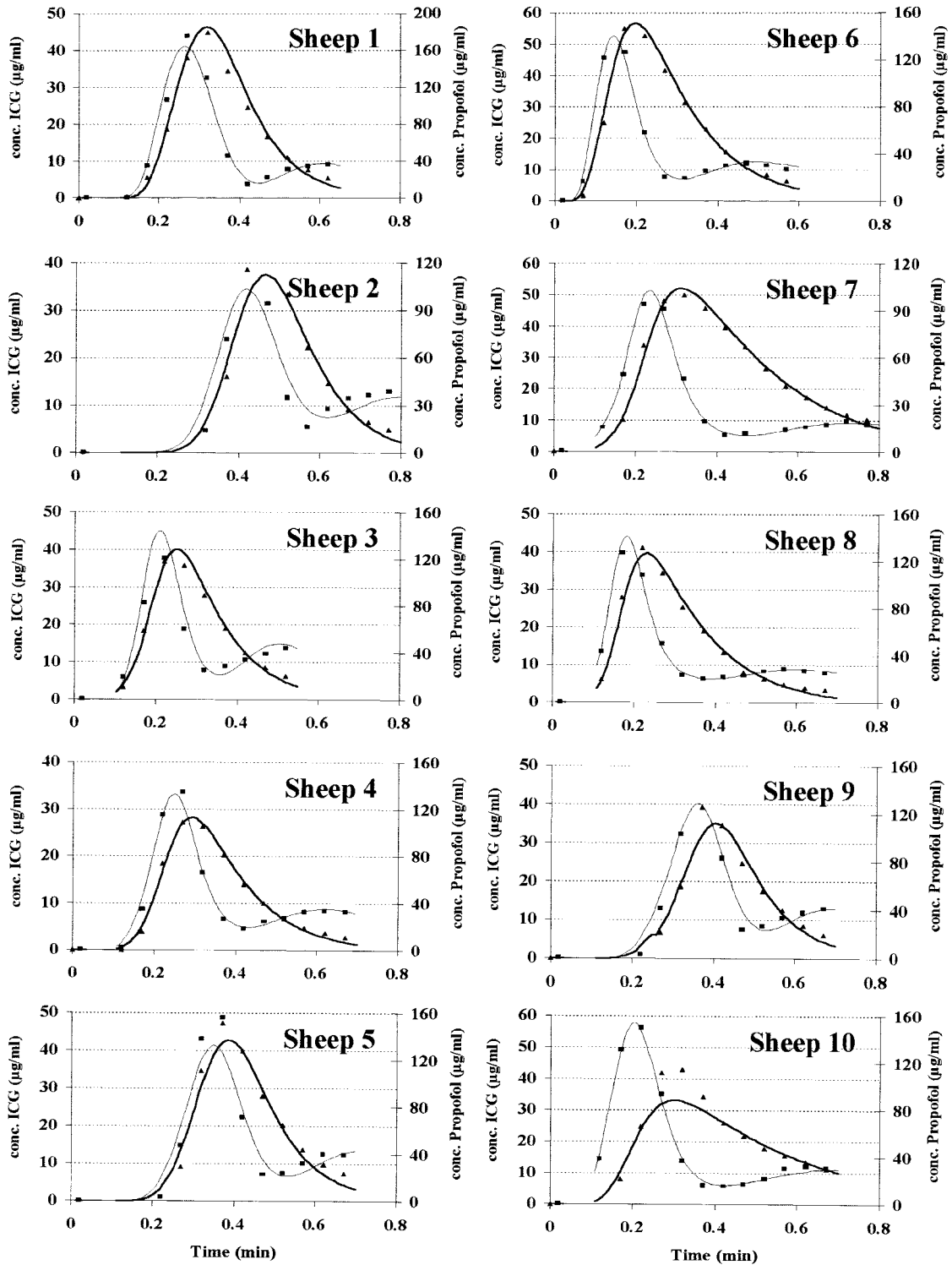


Fig. 4. First-pass fits of indocyanine green (ICG) and propofol for all 10 sheep (squares, measured ICG concentrations; thin line, fit to the ICG data; triangles, measured propofol concentrations; thick line, fit to the propofol data).



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**Table 3. Parameters of the First-pass Kinetics of Propofol Determined with Use of the Central Part of a Recirculatory Model**

Parameter	Mean $\pm$ SD
CO (l/min)	3.90 $\pm$ 0.72*
V <sub>C</sub> (l)	0.66 $\pm$ 0.17*
V <sub>lung</sub> (l)	0.47 $\pm$ 0.16
Cl <sub>El_lung</sub> (l/min)	1.14 $\pm$ 0.23

\* Equal by definition the values for indocyanine green.

had a pulmonary tissue compartment volume (V<sub>lung</sub>) of 0.47  $\pm$  0.16 l, and the elimination clearance from the lung (Cl<sub>El\_lung</sub>) was 1.14  $\pm$  0.23 l/min.

## Discussion

We demonstrated significant first-pass pulmonary uptake and elimination of propofol in sheep after a bolus dose of propofol. The pulmonary uptake and pulmonary elimination of propofol were detected using the central part of a recirculatory model for ICG extended with a pulmonary compartment for pharmacokinetic analysis. We also demonstrated correlations between CO and the ICG model parameters, V<sub>ss</sub>, V<sub>C</sub>, and Cl<sub>ND\_f</sub> of a recirculatory model.

In this study, we were not capable of describing the whole recirculatory model for propofol because concentrations rapidly became undetectable. Consequently, it is theoretically impossible to discriminate between elimination in the lung and distribution into a deep lung compartment. However, for propofol, pulmonary elimination is more likely to occur in sheep than distribution into a deep lung compartment. This is supported by a study in sheep performed by Mather *et al.*,<sup>14</sup> who detected a pulmonary arterial-aortic concentration gradient and undetectable propofol concentrations in lung tissue. The elimination of propofol from the pulmonary compartment was 1.14 l/min. Mather *et al.*,<sup>14</sup> using a mass-balance approach, also found a significant pulmonary clearance of 1.21  $\pm$  1.47 l/min that varied enormously among sheep.

Sheep were chosen for this study because they easily accept immobilization, which was required to allow blood sampling without additional anesthesia. Because blood loss to a maximum of 8 ml/kg is well tolerated<sup>15</sup> and sheep of 45–55 kg were used in the experiments, no problems with changes in blood volume occurred.

The relationship between ICG model parameters and CO confirms earlier results of a study performed in pigs

that received a bolus dose of ICG and alfentanil.<sup>10</sup> In the present study, only Cl<sub>ND\_f</sub> was related to CO, and the slow peripheral blood flow (Cl<sub>ND\_s</sub>) was independent of CO. Cl<sub>ND\_s</sub> is considered to represent the splanchnic circulation,<sup>8</sup> and these results indicate that in the limited range of CO values observed in this study, splanchnic blood flow is a constant independent parameter. In the earlier study in pigs,<sup>10</sup> we found a relation between the Cl<sub>ND\_s</sub> and CO, which is not confirmed in this study. This difference may be a result of the experimental setting, because the experiments in pigs were performed during anesthesia, and CO was pharmacologically manipulated to obtain a wide range of CO values. Anesthetics may influence the peripheral blood flow distribution.

Metabolic processes control the clearance of propofol from the body, with the liver being the principal eliminating organ.<sup>3</sup> Total hepatic blood flow is assumed to approximate 25% of the CO in most animal species under resting conditions.<sup>16</sup> This is in all likelihood also true for our sheep, because the mean CO was 3.9 l/min, and blood flow through the slow peripheral blood compartment, representing splanchnic blood flow, was 0.81 l/min (21%). The total clearance of propofol often exceeds hepatic blood flow, as has been observed in patients.<sup>6</sup> This can only be explained by extrahepatic clearance. Cockshott<sup>3</sup> suggested that because extrahepatic clearance contributes significantly to total propofol clearance, it must take place in an organ receiving a significant fraction of the CO, *e.g.*, the kidneys, lungs, or blood/plasma. The present study confirms this suggestion, at least in sheep.

In a study by Simons *et al.*,<sup>17</sup> 88% of the dose of propofol was recovered in urine as hydroxylated and conjugated metabolites. Although glucuronidation is the main metabolic pathway of propofol excretion, hydroxylation by cytochrome P450 enzymes has also been shown to be involved in the metabolism of propofol.<sup>18</sup> Both hydroxylation and glucuronidation are possible pathways for lung metabolism. Veroli *et al.*<sup>2</sup> have shown that extrahepatic glucuronidation of propofol occurred during anhepatic phase of orthotopic liver transplantation in humans. Pulmonary hydroxylation has been suggested by an *in vitro* study that showed lung and liver biotransformation of propofol to be almost equally fast in rabbits, while both were reduced by an inflammatory reaction.<sup>19</sup> The fact that the activity of cytochrome P450 is inhibited by an inflammatory reaction<sup>20</sup> suggests that cytochrome P450 is involved in the metabolism of propofol in the liver and the lungs. The contribution of pulmonary elimination to the total clearance of propofol

can be significant, as our results show, even if the intrinsic clearance by the lungs is relatively small compared with that of the liver.<sup>21</sup> The lungs receive the total CO, whereas the liver receives only a fraction. Theoretically, propofol, a relatively volatile substance, might also be removed from the lungs by exhalation. However, this pathway is speculative and remains to be investigated.

If a conventional two- or three-compartment model is used for pharmacokinetic analysis, it is not possible to distinguish between elimination by the liver, lungs, kidneys, or other sites. Distinguishing between these different elimination sites is only possible with a physiologic model, allowing investigation of individual organs. A recirculatory model can discriminate between the central part of the body (lungs and heart) and the peripheral part of the body, and it can discriminate between intravascular and extravascular parts of the body. Thus, this model can be valuable when a more precise identification of kinetic processes is required. It allowed us to examine whether elimination of propofol occurs in the lungs without the need for pulmonary artery sampling.

In our model for propofol, we included pulmonary uptake and pulmonary elimination. The first-pass concentration-time curves of propofol were first fitted using a model that only allowed pulmonary uptake into a single pulmonary compartment. Using such a model, SAAM II was incapable of performing a good fitting procedure; all fitted concentrations were higher than the measured concentrations. Including the possibility of pulmonary elimination (or removal into a deep lung compartment) from the lung compartment resulted in a good first-pass fit of propofol.

The first-pass pulmonary uptake of propofol in cats was 60%.<sup>5</sup> That study, using a double-indicator dilution method, did not distinguish between uptake and elimination of propofol and showed a significant effect of halothane and pretreatment with fentanyl, but not of mechanical ventilation, on the pulmonary kinetics of propofol. In the present study, we avoided possible influences of comedication and ventilation on the first-pass pulmonary uptake and elimination of propofol by studying awake, immobilized sheep. For this reason, we decided to give a single induction dose of propofol, which made it impossible to describe propofol pharmacokinetics for the peripheral part of the recirculatory model in the same study, because propofol concentrations rapidly decreased below the detection limit.

Other methods that have been used for determining pulmonary uptake have some major disadvantages. Both arterial and pulmonary arterial concentrations are

needed for system dynamics analysis of pulmonary uptake.<sup>22,23</sup> This is technically and ethically difficult in many patient groups and volunteers. For the recirculatory modeling method, only arterial samples are needed. The other method used frequently for the study of first-pass lung uptake, the double-indicator dilution technique, can only be used to describe the first-pass period. In contrast, the recirculatory modeling method may be used to model pulmonary uptake beyond the first-pass period. Krejcie *et al.*<sup>24</sup> used a recirculatory model for the pulmonary uptake of lidocaine and suggested a method for reasonably estimating the pulmonary disposition kinetics when arterial first-pass pulmonary uptake kinetics are obscured by recirculation.

We have applied the central part of the recirculatory model of ICG for describing pulmonary kinetics of propofol by adding a pulmonary tissue compartment, from which we allowed clearance of propofol, to the first-pass model of ICG. In our experimental setting, we were not capable of discerning between pulmonary clearance of propofol or distribution of propofol into a deep-tissue compartment. However, the results described here and those from the study by Krejcie *et al.*<sup>24</sup> show that recirculatory models can be useful for describing pulmonary kinetics.

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## References

1. Shafer A, Doze VA, Shafer SL, White PF: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *ANESTHESIOLOGY* 1988; 69:348-56
2. Veroli P, O'Kelly B, Bertrand F, Trouvin JH, Farinotti R, Ecoffey C: Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1992; 68:183-6
3. Cockshott ID: Propofol ('Diprivan') pharmacokinetics and metabolism: An overview. *Postgrad Med J* 1985; 61:45-50
4. He YL, Ueyama H, Tashiro C, Mashimo T, Yoshiya I: Pulmonary disposition of propofol in surgical patients (abstract). *ANESTHESIOLOGY* 1998; 89: A511
5. Matot I, Neely CF, Katz RY, Neufeld GR: Pulmonary uptake of propofol in cats: Effect of fentanyl and halothane. *ANESTHESIOLOGY* 1993; 78:1157-65
6. Gepts E, Camu F, Cockshott ID, Douglas EJ: Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; 66:1256-63
7. Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL: The pharmacokinetics of propofol in children using three different data analysis approaches. *ANESTHESIOLOGY* 1994; 80:104-22

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8. Krejcie TC, Henthorn TK, Niemann CU, Klein C, Gupta DK, Gentry WB, Shanks CA, Avram MJ: Recirculatory pharmacokinetic models of markers of blood, extracellular fluid and total body water administered concomitantly. *J Pharmacol Exp Ther* 1996; 278:1050-7
9. Krejcie TC, Jacquez JA, Avram MJ, Niemann CU, Shanks CA, Henthorn TK: Use of parallel erlang density functions to analyze first-pass pulmonary uptake of multiple indicators in dogs. *J Pharmacokin Biopharm* 1996; 24:569-88
10. Kuipers JA, Boer F, Olofsen E, Olieman W, Vletter AA, Burm AGL, Bovill JG: Recirculatory and compartmental pharmacokinetic modeling of alfentanil in pigs: The influence of cardiac output. *ANESTHESIOLOGY* 1999; 90:1146-57
11. Lin HC, Purohit RC, Powe TA: Anesthesia in sheep with propofol or with xylazine-ketamine followed by halothane. *Vet Surg* 1997; 26:247-52
12. Henthorn TK, Avram MJ, Krejcie TC, Shanks CA, Asada A, Kaczynski DA: Minimal compartmental model of circulatory mixing of indocyanine green. *Am J Physiol* 1992; 262:H903-10
13. Avram MJ, Krejcie TC, Niemann CU, Klein C, Gentry WB, Shanks CA, Henthorn TK: The effect of halothane on the recirculatory pharmacokinetics of physiologic markers. *ANESTHESIOLOGY* 1997; 87:1381-93
14. Mather LE, Selby DG, Runciman WB, McLean CF: Propofol: Assay and regional mass balance in sheep. *Xenobiotica* 1989; 19:1337-47
15. Havenaar R, Ritskes-Hoitinga J, Meijer JC, Zwart P: Biologie en zoötechnieken, Proefdieren en dierproeven, 2nd Edition. Utrecht, The Netherlands, Bunge, 1995, pp 20-74
16. Greenway CV, Stark RD: Hepatic vascular bed. *Physiol Rev* 1971; 51:23-65
17. Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, Rowland M: Disposition in male volunteers of a sub-anaesthetic intravenous dose of an oil in water emulsion of 14C-propofol. *Xenobiotica* 1988; 18:429-40
18. Guittion J, Buronfosse T, Desage M, Flinois JP, Perdrix JP, Brazier JL, Beaune P: Possible involvement of multiple human cytochrome P450 isoforms in the liver metabolism of propofol. *Br J Anaesth* 1998; 80:788-95
19. Audibert G, Saunier CG, Du Souich P: In vivo and in vitro effect of cimetidine, inflammation, and hypoxia on propofol kinetics. *Drug Metab Dispos* 1993; 21:7-12
20. Chindavijak B, Belpaire FM, Bogaert MG: In-vitro biotransformation of antipyrine, lignocaine and propranolol in the liver of rats with turpentine-induced inflammation. *J Pharm Pharmacol* 1987; 39:883-6
21. Mehvar R: Relationship of apparent systemic clearance to individual organ clearances: Effect of pulmonary clearance and site of drug administration and measurement. *Pharm Res* 1991; 8:306-12
22. Boer F, Hoefl A, Scholz M, Bovill JG, Burm AGL, Hak A: Pulmonary distribution of alfentanil and sufentanil studied with system dynamics analysis. *J Pharmacokin Biopharm* 1996; 24:197-218
23. Boer F, Olofsen E, Bovill JG, Burm AGL, Hak A, Geerts M, Wetselaar KE: Pulmonary uptake of sufentanil during and after constant rate infusion. *Br J Anaesth* 1996; 76:203-8
24. Krejcie TC, Avram MJ, Gentry WB, Niemann CU, Janowski MP,

Henthorn TK: A recirculatory model of the pulmonary uptake and pharmacokinetics of lidocaine based on analysis of arterial and mixed venous data from dogs. *J Pharmacokin Biopharm* 1997; 25:169-90

## Appendix: Determination of Whole-blood Concentrations of Propofol

The assay was developed by A. A. Vletter, B.Sc., W. Olieman, and A. G. L. Burm, M.Sc., Ph.D., Anesthesia Research Laboratory, Leiden University Medical Center, Leiden, The Netherlands.

Whole-blood concentrations of propofol were determined with high-performance liquid chromatography. The following were added in sequence to 200- $\mu$ l blood samples: 25  $\mu$ l ethanol (or 25  $\mu$ l ethanol containing standard amounts of propofol), 100  $\mu$ l distilled water, and 25  $\mu$ l ethanol containing 75 ng thymol (internal standard). The sample was mixed after each addition. Then 500  $\mu$ l of acetonitrile was added. Subsequently, the sample was vortexed for 3 min and centrifuged for 10 min at 2,000  $\times g$ . Three hundred microliters of the supernatant was transferred into autoinjector vials for high-performance liquid chromatographic analysis, and 20  $\mu$ l was injected.

The high-performance liquid chromatography system consisted of a pump, a fluorescence detector equipped with a 5- $\mu$ l flow cell, a Marathon XT autoinjector, a column thermostat (all Separations Analytical Instruments, Hendrik Ido Ambacht, The Netherlands), a stainless steel column (75  $\times$  4.6 mm) prepacked with ultrasphere C-18, 3  $\mu$ m (Beckman, San Ramon, CA), a Chromeleon chromatography data system (Gynkotec, Germering, Germany), and a Compaq Pentium 2 computer (Compaq Computer Corp., Houston, TX). The column temperature was 40°C. The excitation wavelength was 270 nm, and an emission long-pass cutoff filter of 310 nm was used. The mobile phase consisted of acetonitrile (24% vol/vol), methanol (32% vol/vol), and water (44% vol/vol), to which 0.5 ml trifluoroacetic acid was added per liter. The final pH of the mobile phase was adjusted to 3.0 with 2 N sodium hydroxide. The flow rate of the mobile phase was 1.5 ml/min.

The retention times of thymol and propofol were 3.2 and 6.5 min, respectively. No endogenous compounds were found to interfere with the assay. The detection limit, defined as a signal-to-noise ratio of 3, was 0.04  $\mu$ g propofol per milliliter blood, and 0.11  $\mu$ g/ml could be quantified with acceptable precision. The interday coefficient of variation of the peak height ratios of propofol *versus* thymol, determined over 6 different days using blood from male human volunteers, was 9.8% for the lowest concentration (0.110  $\mu$ g/ml) and < 3.7% in the range of 0.46-13.54  $\mu$ g/ml.

Calibration curves were obtained by weighted (weight factor 1/y<sup>2</sup>) least-squares linear regression analysis of the peak height ratio of propofol/thymol *versus* the concentration of propofol. The calibration lines were linear in the investigated range (0.11-13.54  $\mu$ g propofol per milliliter blood) with correlation coefficients varying from 0.9998 to > 0.9999. The recovery was 85%  $\pm$  4% for propofol and 86%  $\pm$  6% for thymol over the investigated range (0.11-13.54  $\mu$ g propofol per milliliter blood).