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Recirculatory and Compartmental Pharmacokinetic Modeling of Alfentanil in Pigs

The Influence of Cardiac Output

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Background: **Cardiac output (CO) is likely to influence the pharmacokinetics of anesthetic drugs and should be accounted for in pharmacokinetic models. The influence of CO on the pharmacokinetic parameters of alfentanil in pigs was evaluated using compartmental and recirculatory models.**

Methods: **Twenty-four premedicated pigs were evaluated during halothane (0.6–2%) anesthesia. They were assigned randomly to one of three groups. One group served as control. In the other groups, the baseline CO was decreased or increased by 40% by pharmacologic intervention (propranolol or dobutamine). Boluses of alfentanil (2 mg) and indocyanine green (25 mg) were injected into the right atrium. Blood samples were taken for 150 min from the right atrium and aortic root. Arterial concentration–time curves of indocyanine green and alfentanil were analyzed using compartmental models (two-stage and mixed-effects approach) and a recirculatory model, which can describe lung uptake and early distribution.**

Results: **The CO of individual pigs varied from 1.33 to 6.44 l/min. Three-compartmental modeling showed that CO is a determinant of the central compartment volume (V_1, $r^2 = 0.54$), fast peripheral compartment volume (V_2, $r^2 = 0.29$), steady state distribution volume (V_{ss}, $r^2 = 0.29$), fast distribution clearance (Cl_{12}, $r^2 = 0.39$), and elimination clearance (Cl_{10}, $r^2 = 0.51$). Recirculatory modeling showed that CO is a determinant of total distribution volume ($r^2 = 0.48$), elimination clearance ($r^2 = 0.54$), and some distribution clearances. The pulmonary distribution volume was independent of CO.**

Conclusions: **Cardiac output markedly influences the pharmacokinetics of alfentanil in pigs. Therefore, accounting for CO enhances the predictive value of pharmacokinetic models of alfentanil. (Key words: Intravenous anesthetics; performance error.)**

IN human studies, the pharmacokinetic parameters of drugs are usually determined in a broadly homogeneous population with patients or volunteers of the same gender, similar age, and comparable physical condition. In other studies, patient factors such as age, gender, body weight, or all of these have been incorporated with the aim of enhancing the predictive value of the model.[1–3] However, few studies have included physiologic parameters that could be more useful for individualization.

Cardiac output (CO) is likely to influence the distribution of anesthetic drugs. Henthorn *et al.*[4] found that CO largely determined the intercompartmental clearance of alfentanil in humans. In addition, changes in CO are likely to influence liver blood flow, and, therefore, will influence the elimination clearance (Cl_{EI}) of drugs with a high hepatic extraction ratio.[5] The effect of changes in CO on the pharmacokinetics of propofol and the associated clinical implications were described recently.[6,7] The Cl_{EI} of propofol was shown to be flow dependent and, consequently, an increased CO decreased the duration of anesthesia. Cardiac output, therefore, seems to be a potentially valuable parameter for describing the relation between physiology and pharmacokinetics.

Conventional compartmental pharmacokinetic models cannot describe the initial mixing phase and the transit through the lungs.[8,9] To describe the initial mixing phase, Henthorn *et al.*[10] developed a minimal compartmental model of circulatory mixing of indocyanine green (ICG), a marker of intravascular space. This model served as the basis for their complete recirculatory pharmacokinetic model, which can describe the disposition

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of markers of extracellular fluid and total body water,[11] even during the first minutes after injection. Because the recirculatory model can account for the possibility of first-pass pulmonary uptake, it can provide more detailed information than can conventional compartmental models.

Materials and Methods

Experimental Protocol

The study was approved by the local committee for experiments on animals. The study comprised 24 European Landrace pigs between 4 and 5 months old that weighed approximately 40 kg and were used solely for this study. After discontinuation of the experiment, the animals were allowed to recover until they were fit enough to return to the farm. All experiments were performed in the Laboratory of Large Animals of the Leiden University Medical Center.

After an overnight fast, animals were premedicated intramuscularly with azaperone (80 mg), atropine (2 mg), and ketamine (600 mg). Anesthesia was induced by face mask with halothane, to a 2% inspired concentration. After tracheal intubation, the lungs of the pigs were ventilated with 60% nitrous oxide in oxygen. Ventilation was adjusted to maintain a partial pressure of oxygen in arterial blood (Pa_{O_2}) more than 75 mmHg and a partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) between 34 and 38 mmHg. Pancuronium (100 μg/kg) was given *via* an intravenous catheter, and additional pancuronium (25 μg/kg) was administered when required during the experiment. Anesthesia was maintained with halothane, 0.6%. After the experiment, the lungs were ventilated with oxygen until the pig regained consciousness. Intramuscular morphine hydrochloride (0.1 mg/kg) was given, when necessary, for postoperative analgesia.

After establishing an adequate plane of anesthesia, an 8-gauge cannula (Vygon; Vygon, Ecouen, France) was introduced into the right carotid artery under direct vision and advanced into the aortic root. This catheter was used for arterial blood sampling. A second 8-gauge cannula (Vygon) was introduced into the right external jugular vein and advanced into the right atrium. The position was confirmed by inspection of the pressure tracing. This catheter was used for venous blood sampling. Another catheter (CCO-VIP; Intellicath, Baxter-Edwards, Irvine, CA) was introduced through an introducer sheath into the right internal jugular vein and advanced into the pulmonary artery by following the pressure tracing while the catheter was being introduced. This catheter was used for semicontinuous measurement of CO (Vigilance monitor; Baxter-Edwards), measurement of central and pulmonary arterial pressures, and drug injection into the right atrium using the side port of the catheter.

The animals were assigned randomly to one of the three groups before the baseline CO was determined, therefore, the group assignment was independent of their baseline CO value. Cardiac output was measured by thermodilution and, depending on the group allocation, was left unchanged, decreased, or increased. This was performed to ensure a wide range of CO values. The pigs in which CO was to be decreased were given 2 mg propranolol and halothane to a maximum inspired concentration of 2% (range, 1% to 2%) until CO had decreased by 40% below baseline. The pigs in which CO was to be increased were given dobutamine as needed until CO had increased by 40% above baseline. During the experiment, CO was measured semicontinuously by thermodilution to evaluate initial changes of the CO in the hypo- and hyperdynamic groups and to check the stability of CO during the experiment.

The pharmacokinetics of alfentanil and ICG were studied after a bolus injection. The injectate was prepared by mixing 3 ml autologous blood with ICG (25 mg) dissolved in 3 ml solvent and 4 ml alfentanil (2 mg). From this 10-ml mixture, 1 ml was stored for later measurement of the concentration of ICG and alfentanil in the injectate, and the other 9 ml was administered as a bolus injection. The syringe was weighed before and after the injection to allow the injected volume and doses of ICG and alfentanil to be calculated. Blood samples (2 ml) were collected with the aid of a specially constructed computer-controlled syringe pump and fraction collector, which allowed simultaneous sampling of arterial and venous blood. Sampling volume was equal to the sum of the dead space volumes in the catheter and the extension lines to the sampling device. Blood sampling started 2 s before the bolus injection. Samples were taken at 4-s intervals for 30 s. The sampling frequency was decreased to once every 5 s for the next 30 s. Sampling frequency in the second minute was decreased to once every 10 s. Thereafter, sampling was continued at 4, 7, 10, 15, 20, 30, 45, 60, 90, 120, and 150 min after the bolus injection. During the first 10 min, waste samples were taken to clear the system between samples. After 10 min, the sampling device was disconnected and sampling was continued by hand. Before the experiment, a blood sam-

ple of 20 ml was drawn to construct the calibration curves of alfentanil and ICG.

Methods of Analysis

Whole blood alfentanil analysis was performed using capillary gas chromatography.[12] The limit of detection was 0.8 ng/ml, and the coefficient of variation did not exceed 5% in the alfentanil concentration range in this study. Indocyanine green concentrations were measured spectrophotometrically at 805 nm[13] on the day of the experiment. For each experiment, a new reference line was constructed using whole blank blood from the pig and known amounts of ICG. The limit of detection was 1 μg/ml, and the coefficient of variation was 2.6–3.9% for the relevant range of concentrations.

Data Analysis

Early arterial ICG concentrations were used to determine the CO using the indicator dilution method.[14] This value of the CO was used in the final data analysis.

Compartmental Models: Two-stage and Mixed-effects Approaches. For compartmental analysis, only the arterial samples collected at 1, 2, 4, 7, 10, 15, 20, 30, 45, 60, 90, 120, and 150 min were used, because this is a common sampling design for conventional compartmental analysis. Arterial blood concentration *versus* time data of alfentanil were analyzed using conventional open two- and three-compartment mamillary models and iteratively reweighted nonlinear regression analysis for each pig. The parameters of the individual fits were averaged to describe the population. This analysis is called the two-stage approach.

With the same arterial samples that were used in the two-stage approach, population pharmacokinetic data (three-compartment model) were derived using NONMEM (version IV, level 2.1; NONMEM Project Group, University of California, San Francisco, CA).[15] NONMEM analysis was performed using a prediction subroutine (NMVCL; written by S. L. Shafer, Palo Alto VA Medical Center, Palo Alto, CA; available *via* the World Wide Web at URL http://pkpd.icon.palo-alto.med.va.gov) configured with a log-normal variance model of the interindividual error term of the kinetic model parameters (central compartment volume [V_1], fast peripheral compartment volume [V_2], slow peripheral compartmental volume [V_3], elimination clearance [Cl_{10}], rapid distribution clearance [Cl_{12}], and slow distribution clearance [Cl_{13}]) and a log-normal variance model, which is equivalent to a constant relative error for small variance of the intraindividual error term (*i.e.*, measurement error). The best estimation method was selected by comparing the median performance error (MDPE) and the median absolute performance error (MDAPE). The first-order conditional estimation method without "η-ϵ" interaction was used.[15] In NONMEM, the best covariate model included CO for all parameters except Cl_{13}, which was determined by the likelihood ratio test. This analysis is called the mixed-effects approach.

To evaluate the usefulness of incorporating CO in the two-stage approach, the predictive values of CO-corrected and CO-uncorrected (*i.e.*, mean) pharmacokinetic data of the two-stage approach and the predictive values of the mixed-effects model were assessed in individual pigs by analyzing the bias and inaccuracy associated with these data sets.[16] The performance error was calculated for each blood sample as:

$$PE = \frac{(C_p - C_{pred})}{C_{pred}} \times 100$$

where C_p is the measured plasma concentration of alfentanil and C_{pred} is the corresponding predicted plasma concentration. For each pig, the bias of the system was determined as the MDPE over all blood samples and the inaccuracy as the median of the MDAPEs. Subsequently, the median values of the individual MDPEs and MDAPEs were determined for the whole group and for pigs in which CO deviated more then 1 l/min from the mean CO of the entire group.

Recirculatory Models. The pharmacokinetic model used is based on the recirculatory model described by Krejcie *et al.*[11] (fig. 1). In this recirculatory model, the central assumption is that ICG is confined to the intravascular space and thereby defines the intravascular kinetics of other simultaneously injected drugs, in this case alfentanil. The model consists of two parts: the intravascular part described by ICG, and the tissue pool, which describes the extravascular kinetics of the simultaneously administered alfentanil.

The central intravascular part of the model, representing blood flow through the heart and lungs, was described by two combined parallel pathways, a fast and a slow central pathway.[17] The shape of the first-pass concentration–time curve of ICG (*i.e.*, the data before evidence of ICG recirculation) was described by the following equation[18]:

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

where n_1 and n_2 are the numbers of compartments in

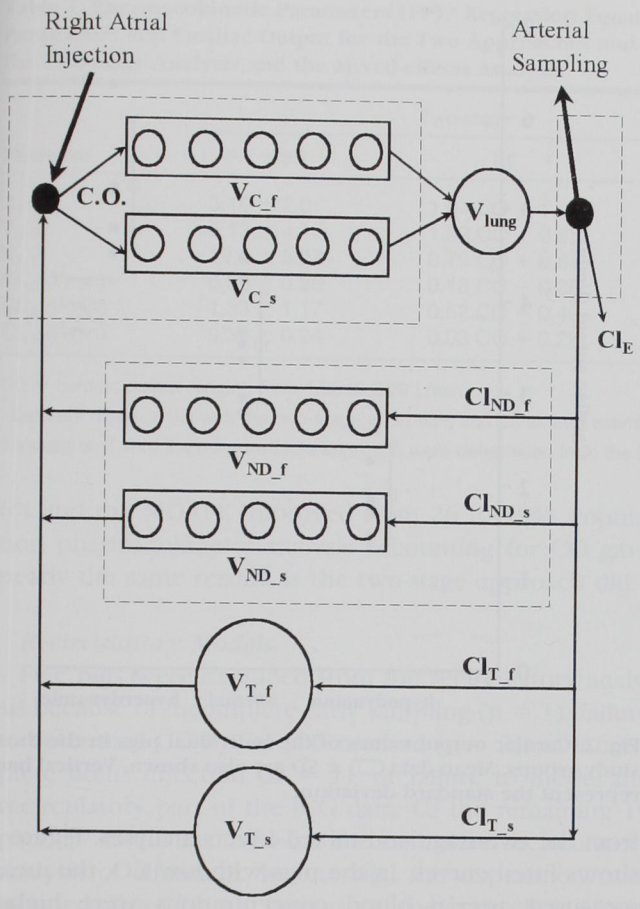

Fig. 1. The recirculatory pharmacokinetic model used to analyze indocyanine green and alfentanil concentration–time relations. The parts in the dashed boxes represent the model for indocyanine green, the intravascular part of the model. The complete model is used to describe the alfentanil pharmacokinetics. Cl_{ND_f} = fast nondistributive; Cl_{ND_s} = slow nondistributive clearance; Cl_{T_f} = fast peripheral tissue clearance; Cl_{T_s} = slow peripheral tissue clearance; C.O. = cardiac output; V_{C_f} = fast central volume; V_{C_s} = slow central volume; V_{ND_f} = fast nondistributive volume; V_{ND_s}; slow nondistributive volume; V_{T_f} = fast peripheral tissue volume; V_{T_s} = slow peripheral tissue volume.

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; A_1 and A_2 are the areas under the first-pass concentration–time curves, determined by the CO and the dose of ICG; $(A_1/(A_1 + A_2)) \cdot 100$ = the percentage of blood flow through the fast central pathway = A_{C_f}; $(A_2/(A_1 + A_2)) \cdot 100$ = the percentage of blood flow through the slow central pathway = A_{C_s}.

This equation is the sum of two Erlang distribution functions, where A_{C_f} and A_{C_s} are the proportional blood flows through the two parallel delay elements. 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 method has been described in detail in an appendix to a recent article of Avram *et al.*[18] The parameters obtained from the Erlang functions were used as fixed parameters in a complete recirculatory model for ICG, including 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 Cl_{EI}. The CO is determined by dividing the dose of ICG by the area under the first-pass concentration–time curve ($A_1 + A_2$). Cardiac output is distributed over the peripheral circuits and the model can, similar to a physiologic model, accommodate differences in CO with redistribution over these two circuits. The model was obtained by an iterative fitting procedure using the SAAM II program (SAAM institute, Seattle, WA).

The intravascular pharmacokinetic parameters of ICG were used to evaluate the arterial alfentanil data by adding to the central intravascular model, a pulmonary tissue compartment (V_{lung}), and two peripheral tissue compartments (characterized by V_{T_f} and Cl_{T_f}, and V_{T_s} and Cl_{T_s}, respectively). In the central circulation, the volume of the lung compartment was reflected by the difference in first-pass ICG and alfentanil pharmacokinetics. The central alfentanil pharmacokinetics are described by a combination of the fixed parameters of the Erlang functions describing the intravascular central ICG pharmacokinetics and one additional parameter accounting for the uptake of alfentanil in the lung, determining the delay of alfentanil compared with ICG. The clearances through the parallel fast and slow peripheral nondistributive circuits for ICG (for which clearances = blood flows) equal the CO.[11] For alfentanil, the ratio between fast and slow peripheral nondistributive clearances equals that for ICG, but the values are not the same as for ICG.

The many tissues in the body are represented by the fast and the slow peripheral tissue compartments. The mean transit time (MTT) determines whether a nondistributive pathway is a fast or a slow pathway and, similarly, whether a distributive pathway represents a rapidly or a slowly equilibrating tissue compartment. With ICG, the MTTs of the central and nondistributive pathways equal the (blood) volumes of the compartments or compartments in series divided by the blood flow through the compartments. With alfentanil, the MTTs of both the

distributive compartments and the nondistributive compartments or compartments in series equal the volumes divided by the nondistributive or distributive clearances. The total recirculatory model for alfentanil, therefore, consists of seven compartments: four nondistributive compartments, two central and two peripheral, described by ICG; and three distributive tissue compartments, two peripheral and one lung compartment. The model also needs two pivot (negligibly small) compartments to allow for the description of sampling and drug injection (fig. 1), because SAAM II does not permit sampling from a nondistributive series of compartments. In the SAAM II analysis, the data were reweighted iteratively over the predicted values.

Statistical Analyses

The CO values of the three groups were compared using one-way analysis of variance. Relations between the CO and the pharmacokinetic parameters were evaluated using standard linear regression. The criterion to reject the null hypotheses was $P < 0.05$. Data are summarized as the mean ± SD unless otherwise specified.

Results

Compartmental Modeling: Two-stage and Mixed-effects Approaches

Four pigs were excluded from the compartmental modeling because measurement of CO with the ICG method failed (n = 2) or because concentration–time profiles of alfentanil could not be described adequately using a three-compartmental model (n = 2). The average weight of the remaining 20 pigs was 38.1 ± 1.6 kg. Cardiac output values for all 20 pigs ranged from 1.38 to 6.29 l/min (3.33 ± 1.37 l/min) and were evenly distributed (fig. 2). In individual pigs, the coefficient of variation of CO, measured semicontinuously using the thermodilution technique, was less than 10% over 150 min and approximately 5% during the first 10 min, and it was independent of group allocation. Heart rate and blood pressure were stable during the experiments (*i.e.*, coefficients of variations were less than 10%).

In the 20 pigs, the whole blood alfentanil concentration–time curves were best described by a triexponential equation reflecting a three-compartment open model. A three-compartment model described the concentration–time curve better than did a two-compartmental model, according to Schwarz criterion and Akaike criterion.[19] Table 1 shows values of the pharmacokinetic parameters

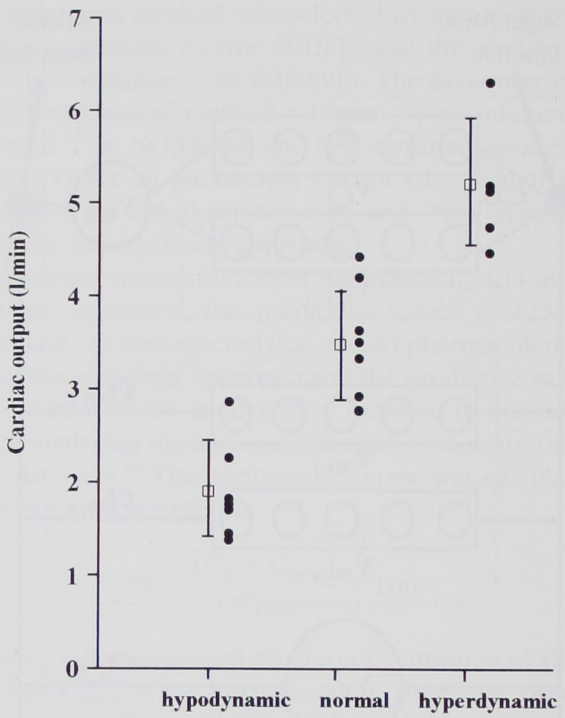

Fig. 2. Cardiac output values of the individual pigs in the three study groups. Mean data (□) ± SD are also shown. Vertical bars represent the standard deviation.

from the two-stage and mixed-effects analyses. Figure 3 shows fitted curves. In the pigs with low CO, the mean measured arterial blood concentrations were higher than those in the other groups at all times. Similarly, the pigs with high CO had lower mean alfentanil concentrations than the pigs from the other groups at all times. As a result of these differences, the pharmacokinetic parameters should also differ with changes in CO. Figure 4 shows the correlations between CO and the pharmacokinetic parameters of the two-stage approach. There was a significant correlation between CO and the model parameters V_1, V_2, Cl_{10}, and Cl_{12}. In addition, there was a significant correlation between CO and steady state distribution volume (V_{ss}) (V_{ss} = 3.42 CO + 10.3, r^2 = 0.30). However, V_3 and Cl_{13} were not influenced significantly by changes in CO. Table 1 presents the regression equations describing the relation between CO and kinetic parameters for the two-stage and mixed-effects analyses, together with the coefficients of determination.

Table 2 shows bias and inaccuracy data. Overall, the pharmacokinetic data corrected for CO resulted in a somewhat better performance than the uncorrected data with the two-stage approach. For the pigs with extremely low or high CO, the MDPE improved from 16 to

Table 1. Pharmacokinetic Parameters (PP),* Regression Equations (RE) Describing the Relationship between Pharmacokinetic Parameters and Cardiac Output for the Two Approaches and Corresponding Coefficients of Determination (r^2)† Obtained with the Two-stage Analysis and the Mixed-effects Analysis

Parameter	Two-stage			Mixed-effects		
	PP ± SD	RE	r^2	PP ± SE	RE	r^2
V_1 (l)	3.10 ± 2.0	1.04 CO − 1.37	0.54	2.69 ± 0.70	1.09 CO − 0.94	0.58
V_2 (l)	6.13 ± 4.16	1.59 CO + 0.83	0.29	4.51 ± 0.73	1.96 CO − 2.02	0.84
V_3 (l)	12.5 ± 5.28	0.79 CO + 9.84	0.04	12.2 ± 1.47	0.91 CO + 9.17	0.25
Cl_{10} (l/min)	0.69 ± 0.26	0.13 CO + 0.26	0.51	0.69 ± 0.06	0.16 CO + 0.16	0.58
Cl_{12} (l/min)	1.33 ± 1.17	0.52 CO − 0.40	0.39	1.02 ± 0.11	0.33 CO − 0.08	0.95
Cl_{13} (l/min)	0.33 ± 0.24	0.03 CO + 0.23	0.03	0.34 ± 0.06	−0.01 CO + 0.37	0.03

CO = cardiac output ranging from 1.38 to 6.29 L/min.

* Data are mean ± SD with the two-stage approach, and parameter estimates ± standard error with the mixed-effects approach.

† Values of r^2 with the mixed-effects approach were determined from the individual Bayesian estimates.

6% and the MDAPE improved from 26 to 19%. Population pharmacokinetic analysis accounting for CO gave nearly the same results as the two-stage approach did.

Recirculatory Models

Five pigs were excluded from the recirculatory analysis because of incomplete early sampling (n = 1), failure to determine CO by the ICG method (n = 2), an incomplete bolus injection (n = 1), or failure to model the recirculatory part of the ICG data. Of the remaining 19 pigs, 17 could be used for the complete recirculatory analysis of alfentanil. In one pig, the experiment was stopped after 120 min because of the poor clinical condition of the pig. In the other pig, the recirculatory model could not fit the concentration–time curve of alfentanil when the ICG data were used.

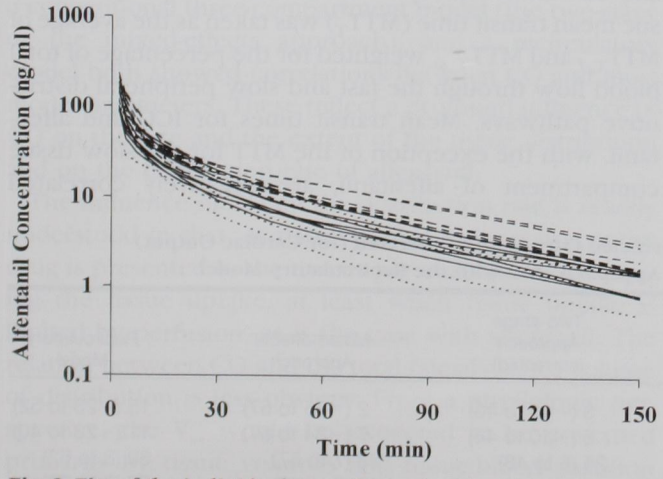

Fig. 3. Fits of the individual pigs obtained with a three-compartmental model using the two-stage approach. —— = control group (n = 8); — — = propanolol group (low cardiac output, n = 7); and - - - = dobutamine group (high cardiac output, n = 5).

The concentration-*versus*-time relation during the early mixing phase after drug injection differs for alfentanil and ICG (fig. 5). Figure 6 shows the fitted curves of alfentanil for the first 2 min of all animals. In this figure, the difference in appearance of the first pass peak as a result of CO is seen. For the central part of the model of alfentanil, the number of compartments in series, the volume of these compartments, and the fraction of the flow through these compartments was, by definition, the same as for ICG, for which the central parameters were determined using the Erlang functions. The shape of the alfentanil and ICG curves is different because alfentanil distributes into lung tissue but ICG does not.

Tables 3, 4, and 5 show the pharmacokinetic parameters of ICG and alfentanil as determined by the recirculatory model and their relations with CO. In 13 pigs, two peripheral tissue compartments could be discriminated, whereas in four pigs (all from the low CO group) only one peripheral tissue compartment could be identified.

Table 3 shows the volumes of all compartments. The volume of the central compartments of ICG and alfentanil, V_{ss} of ICG and alfentanil, and the volumes of the slow distributive compartment and the total peripheral distributive compartment of alfentanil were strongly correlated with CO. The volume of the slow nondistributive compartment of ICG was moderately correlated with CO. Other volumes, including the pulmonary distributive volume of alfentanil, were not correlated with CO.

Table 4 shows the clearances for all compartments. Clearances of central compartments and the lung compartment are not shown, because these are assumed to equal CO, indicating that there is no central elimination of either ICG or alfentanil, which is inherent to the method we used for the central part of the model. For

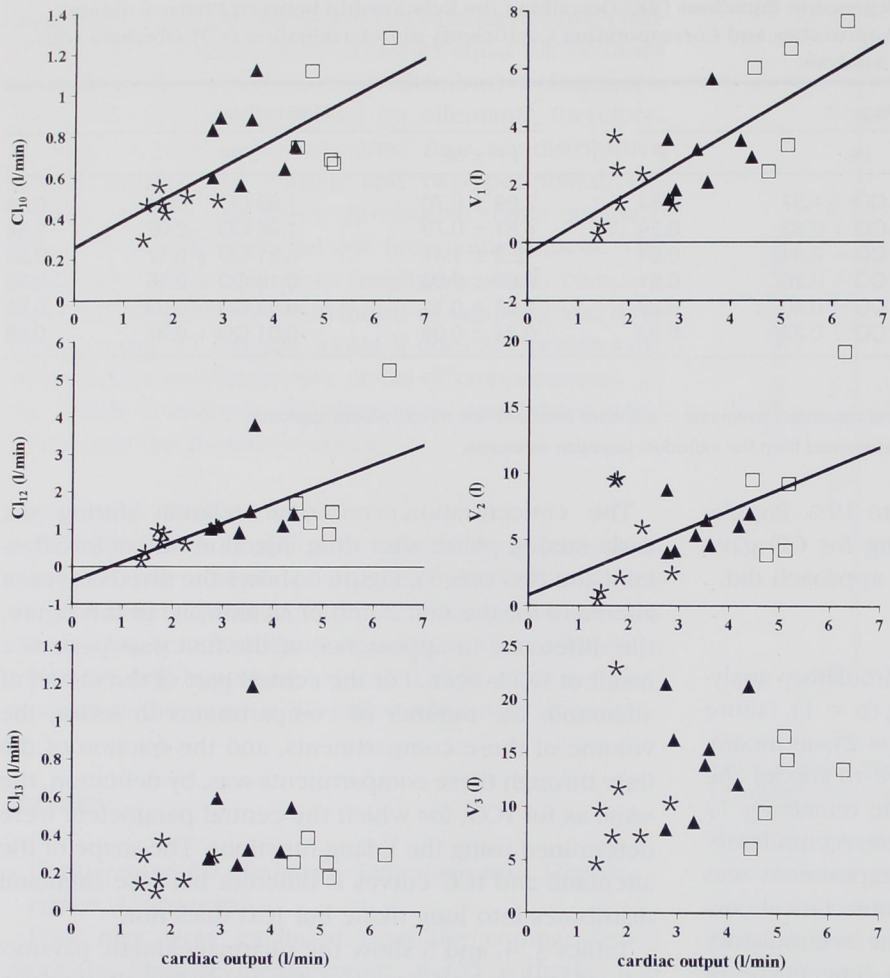

Fig. 4. Regression lines, showing the correlations between pharmacokinetic parameters and cardiac output (in l/min). ▲ = control group; * = propanolol group (low cardiac output); and □ = dobutamine group (high cardiac output).

ICG, the clearances of both nondistributive compartments and for alfentanil the Cl_{EI} the fast and slow peripheral distributive clearance, and the total peripheral distributive clearance were strongly correlated with CO. The clearance of the fast nondistributive compartment of alfentanil was moderately correlated with CO.

Table 5 shows values of MTT for all nondistributive and distributive compartments. The total peripheral tissue mean transit time (MTT_T) was taken as the average of MTT_{T_f} and MTT_{T_s}, weighted for the percentage of total blood flow through the fast and slow peripheral distributive pathways. Mean transit times for ICG and alfentanil, with the exception of the MTT for the slow tissue compartment of alfentanil, are negatively correlated

Table 2. Bias (MDPE) and Inaccuracy (MDAPE) Obtained with Uncorrected (Mean) and Corrected (for Cardiac Output) Pharmacokinetic Data with the Two-stage Approach, Mixed-effects Approach, and with the Recirculatory Model

		Two-stage Approach (uncorrected)	Two-stage Approach (corrected)	Mixed-effects Approach	Recirculatory Model
MDPE (%)	all pigs	9 (−48 to 64)	3 (−40 to 48)	2 (−35 to 67)	15 (−23 to 52)
	High and low CO only*	16 (−48 to 64)	6 (−40 to 48)	7 (−34 to 67)	11 (−23 to 40)
MDAPE (%)	all pigs	26 (12 to 64)	25 (6 to 48)	23 (7 to 67)	30 (8 to 62)
	High and low CO only*	26 (15 to 64)	19 (6 to 48)	22 (7 to 67)	32 (8 to 62)

Data are median (range) and values are given for all pigs and for the pigs with a high and low cardiac output (*n = 12) that differed more than 1 L/min from the mean cardiac output (3.33 L/min).

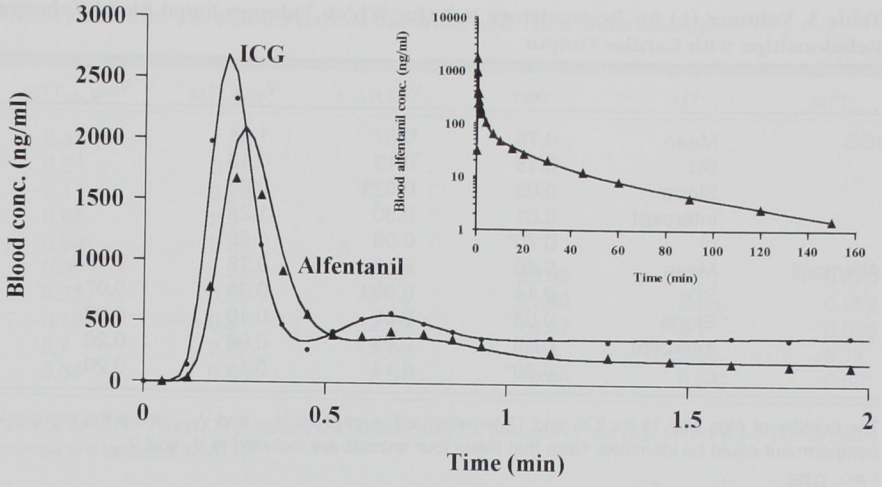

Fig. 5. The concentration–time relations of indocyanine green (ICG) and alfentanil in an individual pig, during the first 2 min after the bolus injection. In the inset, the concentration–time relation for alfentanil in the same pig is shown for the entire experiment. The lines describe the fits of the recirculatory model for ICG and alfentanil. The concentrations of ICG, measured and fitted, are corrected for the larger bolus dose given. The upper line describes the fit of the recirculatory model for ICG, and the lower line describes the fit of the recirculatory model for alfentanil. The dots represent the measured ICG concentrations, and the triangles represent the measured alfentanil concentrations.

with CO, indicating significant flow dependency of the pharmacokinetics of both drugs. In the slow tissue compartment of alfentanil, the decrease in clearance is compensated by the decrease in volume, resulting in an unchanged MTT.

Table 2 shows the MDPE and the MDAPE of the recirculatory model. The MDPE and the MDAPE were calculated for the same alfentanil blood concentrations that were used in the conventional compartmental analyses.

Discussion

We found that CO has a significant influence on the concentration–time curve after administration of a bolus dose of alfentanil in pigs. Pharmacokinetic analysis using a conventional three-compartment model (the two-stage or the mixed-effects approach), and a recirculatory model both showed correlations between CO and most model parameters. These reflect a profound influence of CO on the rate and the extent of the tissue distribution and on the elimination rate of alfentanil.

The influence of CO on the distribution rate is readily understood in that, as tissue perfusion increases, more drug is presented to the tissues per unit of time, increasing the tissue uptake, at least when tissue uptake is limited by perfusion, as is the case with alfentanil. The relation between CO and the total (steady state) volume of distribution is less obvious. From a physiologic perspective, the V_{ss} would be expected to be governed primarily by tissue volumes and tissue:blood partition coefficients, and it is difficult to conceive how CO could alter these factors. However, a relation between CO and V_{ss} has been reported for other anesthetics. For example, Benowitz *et al.*[20] showed that, when the CO was increased with isoproterenol, the initial volume and V_{ss} of lidocaine were increased. Similarly, in a study that evaluated the influence of dexmedetomidine on the thiopental dose requirement,[21] the total distribution volume was decreased compared with that in other studies. This was considered to be a result of a decreased CO, which was induced by dexmedetomidine.

When considering the relation between CO and the elimination rate of alfentanil, it becomes important also to consider liver perfusion. Total hepatic blood flow in most animal species is assumed to approximate 25% of the CO at resting conditions.[22] In our pigs, the calculated Cl_{EI} of alfentanil was approximately 20–30% of the CO, and this fraction was independent of the value of the CO.

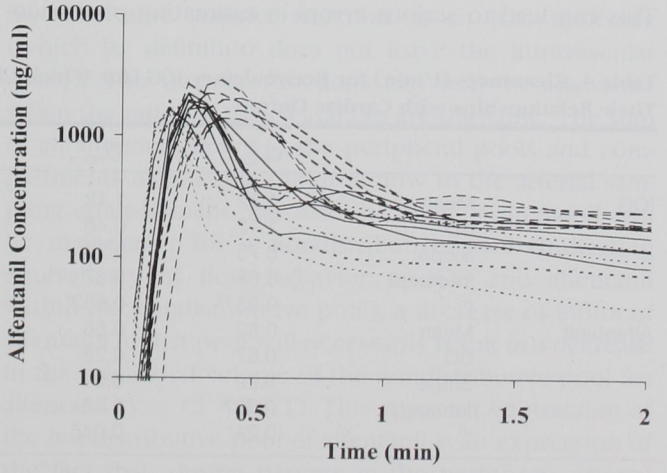

Fig. 6. Fits of the individual pigs obtained with a recirculatory model showing the first 2 min. —— = control group (n = 6); — — = propanolol group (low cardiac output, n = 6); and - - - = dobutamine group (high cardiac output, n = 5).

Table 3. Volumes (L) for Recirculatory ICG (for Which Volumes Equal Blood Volumes) and Alfentanil Pharmacokinetics and Their Relationships with Cardiac Output

		V_C	V_{ND_f}	V_{ND_s}	V_{lung}	V_{T_f}	V_{T_s}	V_T	V_{ss}
ICG	Mean	0.79	0.37	1.41					2.58
	SD	0.15	0.13	0.18					0.32
	Slope	0.08	0.023	0.06					0.17
	Intercept	0.51	0.30	1.22					2.03
	r^2	0.70*	0.08	0.26*					0.62*
Alfentanil	Mean	0.80	0.19	0.73	0.188	4.24	12.24	15.13	17.03
	SD	0.14	0.093	0.33	0.07	2.47	5.64	5.12	5.17
	Slope	0.08	−0.02	−0.10	−0.02	−0.60	3.10	2.61	2.57
	Intercept	0.55	0.27	0.96	0.26	6.54	0.41	6.44	8.48
	r^2	0.69*	0.14	0.1	0.20	0.11	0.57*	0.54*	0.48*

The number of pigs was 19 for ICG and 17 for alfentanil, except for V_{T_f} and V_{T_s} where the number was 13, because in four pigs only one peripheral tissue compartment could be identified. Note that these four animals are included in V_T and V_{ss}.

* $P < 0.05$.

This suggests that the Cl_{EI} of alfentanil is flow limited in pigs and, therefore, would be expected to change in proportion with CO. This was reported after the administration of norepinephrine[23] and after hemorrhage.[22] For propofol and lidocaine, which are other drugs with a flow-limited clearance, an increase in Cl_{EI} with increasing CO has been observed.[20,24]

For the analysis of CO effects on the distribution and elimination of alfentanil, a recirculatory model and conventional compartmental models were used. The former model is a satisfactory alternative to more complicated ones (*e.g.*, physiologic models). One of the assumptions of conventional compartmental models is instantaneous complete mixing, which implies that such models cannot accurately describe the initial distribution and transit through the lung in the first minutes after injection.[25] This can lead to serious errors in estimating pharmacokinetic parameters, especially the central volume.[8] The blood sampling schedule[9] and the timing of the first sample can have an important influence on the estimated volume of the central compartment. For drugs with a fast onset of action, this is an important shortcoming, because the onset of effect may occur before mixing is complete. For these drugs, it can be difficult to determine the pharmacokinetic–pharmacodynamic relation during the onset period using conventional compartmental models to determine pharmacokinetics. Some drugs also undergo significant first-pass pulmonary uptake, which can be important during the first minutes after administration, especially for drugs with very fast effects. Significant first-pass pulmonary uptake of alfentanil has been shown in pigs[26] and to a lesser extent in patients.[13]

The recirculatory model applied in this study, which is

Table 4. Clearances (l/min) for Recirculatory ICG (for Which Clearances Equal Blood Flows) and Alfentanil Pharmacokinetics and Their Relationships with Cardiac Output

		Cl_{ND_f}	Cl_{ND_s}	Cl_{EI}	Cl_{T_f}	Cl_{T_s}	Cl_T	ΣCl
ICG	Mean	1.72	1.18	0.37				3.27
	SD	1.12	0.46	0.088				1.49
	Slope	0.73	0.25	0.027				
	Intercept	−0.65	0.37	0.28				
	r^2	0.937*	0.632*	0.21				
Alfentanil	Mean	0.82	0.56	0.66	0.97	0.59	1.29	3.33
	SD	0.67	0.28	0.23	0.54	0.8	1.17	1.49
	Slope	0.22	0.04	0.11	0.27	0.39	0.63	
	Intercept	0.087	0.43	0.28	−0.058	−0.91	−0.8	
	r^2	0.24*	0.046	0.54*	0.47*	0.45*	0.63*	

The number of pigs was 19 for ICG and 17 for alfentanil, except for Cl_{T_f} and Cl_{T_s} where the number was 13, because in four pigs only one peripheral tissue compartment could be identified. Note that these four animals are included in Cl_T and ΣCl. ΣCl was by definition equal to cardiac output; therefore, no correlation is given.

* $P < 0.05$.

Table 5. Mean Transit Times (min) for Recirculatory ICG and Alfentanil Pharmacokinetics and Their Relationships with Cardiac Output

		MTT_C	MTT_{ND_f}	MTT_{ND_s}	MTT_{T_f}	MTT_{T_s}	MTT_T	MTT_{lung}
ICG	Mean	0.28	0.31	1.38				
	SD	0.083	0.21	0.55				
	Slope	−0.03	−0.11	−0.28				
	Intercept	0.45	0.68	2.3				
	r^2	0.88*	0.64*	0.57*				
Alfentanil	Mean	0.27	0.31	1.38	6.02	38.96	16.91	0.074
	SD	0.084	0.22	0.58	4.14	21.99	8.55	0.052
	Slope	−0.03	−0.12	−0.3	−2.28	−4.57	−4.7	−0.029
	Intercept	0.45	0.7	2.37	14.72	56.4	32.56	0.17
	r^2	0.87*	0.64*	0.58*	0.57*	0.08	0.63*	0.63*

The number of pigs was 19 for ICG and 17 for alfentanil, except for MTT_{T_f} and MTT_{T_s} where the number was 13, because in four pigs only one peripheral tissue compartment could be identified. Note that these four animals are included in MTT_T.

* $P < 0.005$.

derived from the recirculatory model used by Krejcie *et al.*,[11] overcomes many of these shortcomings. This model can describe the initial mixing and the transit through the lungs that occur in the first minutes after injection. In contrast to their model, which determines lung uptake by comparing the areas under the first-pass curves separately from the recirculatory data, our model included a distributive tissue compartment in the central part of the model, next to two central nondistributive compartments, to allow the pulmonary uptake to be modeled. With this modification, pulmonary uptake can be determined without having to take high-frequency pulmonary arterial blood samples (in addition to high-frequency arterial blood samples[26]), and recirculation data can be used to determine MTTs of drugs in the pulmonary tissue and the disappearance rate from the lungs. Using this model, however, implies very high-frequency sampling of arterial blood during the first-pass period. The mean distribution volume of alfentanil of the lung compartment in this study was 188 ml, which is similar to the volume found in a previous study with alfentanil in pigs using a system dynamics analysis (V_{lung} = 173 ml).[26] Although the pulmonary distribution volume is small, significant amounts of alfentanil may be retained by the lungs after a bolus injection, be it for a short period, because the MTT through the lungs is quick (0.07 min). The total blood volume found in this study is the sum of the volumes of the compartments of ICG, for the recirculatory analysis, and was 2.58 ± 0.32 l or 67 ± 8.4 ml/kg. This corresponds with the reported blood volume in pigs of 74 ml/kg.[27] The central blood volume was 0.794 l, which is 31% of the total blood volume.

In the recirculatory analysis, the MTT is determined by the volume of a compartment divided by the flow through that compartment (MTT = V/Cl). In our study, all MTTs (except MTT_{T_s}) were highly and inversely correlated with CO. That is, with a higher CO the clearance or flow through a compartment increases relatively more compared with the volume of that compartment. There is a positive correlation between Cl_{EI} and CO for alfentanil, therefore, in states of low CO, the blood concentrations of alfentanil will remain high for a longer time (fig. 3). This also prolongs the MTT of the peripheral compartments for alfentanil with a low CO.

In our recirculatory analysis, the intravascular kinetics of alfentanil were assumed to be identical to that of ICG, and therefore could be described by the two nondistributive circuits composed of V_{ND_f} and V_{ND_s}. An alfentanil molecule that does not leave the intravascular space has the same transfer function as an ICG molecule (which by definition does not leave the intravascular space). The transfer functions can only be the same when the ratios of the clearances are the same. The sum of all alfentanil flows to the peripheral pools and compartments must equal the drug flow to the arterial sampling compartment. Because the MTT of alfentanil will be maintained for a nondistributive pool (indicating equivalency of flow behavior of ICG and alfentanil within the nondistributive pool), a decrease of influx of alfentanil in that pool will necessarily result in a decrease in the calculated volume of the nondistributive pool for alfentanil ($V = Cl \times MTT$). This apparent contraction of the nondistributive pool of alfentanil is an expression of the fact that, during passage in the periphery, arterial concentrations are decreased by uptake in the tissue, decreasing the amount of alfentanil in the nondistributive pool. Because the amount of alfentanil in that pool

is calculated by multiplying the volume of the pool by the arterial concentrations, the decrease in the amount of alfentanil in the nondistributive pool can be expressed only by a decrease in the volume of the nondistributive pool. This explains why the volume of the nondistributive alfentanil pool is always less than that of the ICG pool.

The pharmacokinetics of alfentanil in pigs are equally well described by a three-compartmental model that includes CO in the model parameters and by a mixed-effects model as judged by bias (MDPE) and inaccuracy (MDAPE). The mixed-effects model did not further improve the ability to describe the observations. Comparison of the different analysis methods, however, is difficult, and the best method for pharmacokinetic data analysis depends on the study design.[28] To allow comparison of the three models, the performance of the recirculatory model was determined for the same alfentanil concentrations used in the three-compartmental approaches. Therefore, the values for bias and inaccuracy shown only give an indication about the performance of recirculatory models to describe the peripheral tissue compartments.

To determine the influence of CO on the pharmacokinetic parameters, we manipulated CO by pharmacologic interventions to obtain a wide range of CO values. A similar range of outputs also could have been obtained by nonpharmacologic manipulation of CO (*e.g.,* by withdrawing significant amounts of blood or by administering crystalloids or colloids), but would have changed the initial volume of distribution and protein binding. The pigs in the hypodynamic group received a higher halothane concentration (range, 1% to 2%) than the pigs in the other two groups (0.6%). Theoretically, halothane could affect the clearance of alfentanil by altering liver perfusion or by causing enzyme inhibition. The change in the pharmacokinetic parameters because of changes in CO or by enzyme inhibition cannot be separated. The relations between CO and the elimination clearance of alfentanil were linear (fig. 4) and, considering that both the normal and the hyperdynamic group received the same halothane concentration, this suggests an influence of halothane on liver perfusion rather than on enzyme activity.

In our analysis, we used CO calculated by the indicator dilution method rather than CO measured by thermodilution. The CO measured by dye dilution (CO_{ICG}) was significantly less than the CO measured by thermodilution (CO_{th}), but the methods showed a strong correlation ($CO_{ICG} = 0.61 \times CO_{th} + 0.52$; $r = 0.92$). The pulmonary artery catheter used in our experiments was designed for use in humans, so possibly the length of the catheter was not optimal for these pigs. The CO measured by dye dilution therefore was likely to be more accurate in the pigs. We used semicontinuous CO measurement with thermodilution during the experiment to evaluate the changes when CO was manipulated and to analyze the stability of the CO. An influence of alfentanil on CO, which could arise from the higher peak plasma alfentanil concentrations in pigs with a low CO, was not observed.

In the experiments, central venous blood samples from the right atrium were taken to measure separately the central (or lung) transfer function and the peripheral transfer function in the hope of obtaining more information about the shape of the separate parts of the body transfer function.[29] Unfortunately, we could not do this, because right atrium mixing was incomplete, resulting in venous concentrations that were higher than the arterial concentrations taken at the same time.

Can our observations in pigs be extrapolated to humans? As far as the distribution of alfentanil is concerned, we would expect qualitatively similar changes with increasing CO in humans and pigs. In a study of the relation between alfentanil distribution kinetics and CO in humans, Henthorn *et al.*[4] found that the tissue distribution of alfentanil was largely determined by CO. However, as far as the Cl_{EI} is concerned, the relatively small clearance of alfentanil compared with hepatic blood flow in humans would be expected to result in a much less profound influence of changes in CO and liver perfusion in humans than in pigs, in which the clearance of alfentanil approaches hepatic blood flow.

We have shown that CO is an important independent factor that influences the pharmacokinetics of alfentanil. Incorporation of CO improved the predictive value of the model, particularly when CO deviates markedly from normal values. Therefore, inclusion of CO as an independent parameter would be appropriate and would allow better individualization of the model and dosing regimens for individual patients, particularly when patients have low or high CO. We have also shown that recirculatory models are useful tools for investigating the influence of a variable CO on pharmacokinetic parameters. These recirculatory models can describe the pharmacokinetics of an intravascular marker, such as ICG. Parameters for the intravascular pharmacokinetics of the marker can be incorporated in a recirculatory model describing the drug of interest, in this case alfentanil. Distribution can be described from the moment of injec-

tion, including initial mixing, pulmonary uptake, and the influence of CO on the redistribution of blood flow over the different pathways in the body.

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