Influence of Cardiac Output on the Pharmacokinetics of Sufentanil in Anesthetized Pigs

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ABSTRACT

Background: Sufentanil is used for general anesthesia and analgesia. The study aim was to determine the effect of pharmacologically induced changes in cardiac output on the pharmacokinetics of sufentanil in anesthetized pigs.

Methods: Twenty-four pigs were randomly assigned to low, high, and control cardiac output groups. Cardiac output was decreased or increased from baseline by at least 40%, or maintained within ± 10% of baseline, respectively. Sufentanil was administered as a bolus followed by a continuous infusion for 120 min. Timed arterial samples were drawn for sufentanil concentration measurements.

Results: Data from 20 animals were analyzed. The cardiac outputs (means ± SD) were 2.9 ± 0.7, 5.4 ± 0.7, and 9.6 ± 1.6 l/min in the low, control, and high cardiac output groups, respectively. The parameters of the two-compartment pharmacokinetic model for these cardiac outputs were: CL1: 0.9, 1.2, and 1.7 l/min; CL2: 0.9, 3.1, and 6.9 l/min; V1: 1.6, 2.9, and 5.2 l; and V2: 27.5, 47.0, and 79.8 l, respectively. Simulated sufentanil doses to maintain a target plasma concentration of 0.5 ng/ml for 3 h were 99.5, 128.6, and 157.6 μg for cardiac outputs of 3, 5, and 7 l/min, respectively. The context-sensitive half-times for these cardiac outputs increased from 3.1 to 19.9 and 25.9 min, respectively.

Conclusions: Cardiac output influences the pharmacokinetics of sufentanil. Simulations suggest that in the case of increased cardiac output, the dose should be increased to avoid inadequate drug effect at the expense of prolonged recovery, whereas for low cardiac output the dose should be reduced, and a faster recovery may be expected. **(Anesthesiology 2018; 128:912-20)**

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INITIAL systemic arterial concentrations of an intravenously administered drug are inversely related to cardiac output (CO), which largely determines the intercompartmental clearances of the drug.[1,2] For drugs with a high hepatic extraction ratio, changes in CO affect liver blood flow and therefore influence their elimination clearance.[3] Although experimental results support the influence of CO on pharmacokinetics, this effect has been studied for few drugs used for general anesthesia.[1,4,5]

Sufentanil is a synthetic opioid with an analgesic potency of about five to ten times higher than fentanyl. It is clinically used as an intravenous agent for general anesthesia and postoperative analgesia and as an analgesic adjunct for epidural anesthesia during labor and delivery. Previous studies in surgical patients reported a hepatic extraction ratio for sufentanil of at least 0.8.[6] Therefore, changes in CO may influence not only intercompartmental clearances but also the elimination clearance and therefore both initial and steady state systemic arterial concentrations of sufentanil. These assumptions are supported by clinical observations that showed a significant impact of CO changes on sufentanil pharmacokinetics during cardiac surgery with cardiopulmonary bypass.[7–9]

Therefore, our primary aim was to investigate whether changes in CO influence systemic arterial concentrations of sufentanil in anesthetized pigs. Second, we developed mammillary compartmental pharmacokinetic models from the derived plasma concentrations of sufentanil and analyzed the relationship between CO and estimated parameters of the best model. Additionally, we investigated whether CO as a covariate increases the predictive value of the pharmacokinetic model.

What We Already Know about This Topic

- Changes in cardiac output may affect not only the distribution of a drug but also its elimination clearance if it has a high hepatic extraction ratio
- Changes in the pharmacokinetics of a drug resulting from changes in cardiac output may affect both early and steady-state arterial drug concentrations as well as its context-sensitive half-times

What This Article Tells Us That Is New

- In 20 anesthetized pigs randomly assigned to have the pharmacokinetics of intravenously administered sufentanil studied under low, high, or normal cardiac output conditions, sufentanil intercompartmental clearance, compartmental volumes, and elimination clearance increased with cardiac output
- As a result of cardiac output-related changes in pharmacokinetics, simulated sufentanil doses required to maintain a target plasma concentration increased with increasing cardiac output, as did its context-sensitive half-times

Materials and Methods

This study was performed in accordance with the guidelines laid out in the Guide for the Care and Use of Laboratory

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). The results have been presented in part at the International Conference on Opioids, Boston, Massachusetts, June 5–7, 2016. This is a 2017 Frontiers in Opioid Pharmacotherapy Symposium article.

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Animals[10] between February and April 2013 at the Franz-Penzoldt-Zentrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. The study was approved by the designated institutional veterinarian for animal welfare and the local Animal Research Authority (Regierung von Mittelfranken, Ansbach, Germany, AZ 54-2532.1-34/12).

Animal Care, Management, and Anesthesia

Twenty-four immature domestic female pigs (German Landrace, 16 weeks of age) were included in the study. The animals were acclimatized for 2 weeks in the laboratory housing area. Food was withdrawn 6 to 8 h before the study, whereas water was available at all times.

At the investigation day, the animals were randomized to one of the three experimental groups: control, low, or high CO. All animals were sedated within the housing area with midazolam 1 mg/kg intramuscularly (Dormicum; Hoffman-La Roche, Germany) and ketamine 10 mg/kg intramuscularly (Ketavet; Pfizer Pharma, Germany). The sedated animals were weighed and transported into the laboratory operation room, where a 20-gauge intravenous cannula was placed into an ear vein, and an infusion of Ringer's solution was started at 10 ml · kg^{-1} · h^{-1}. Vital signs were continuously monitored using a three-lead electrocardiogram and a transcutaneous pulse oximetry (SC9000 XL; Siemens AG, Germany). After induction of anesthesia with ketamine 0.5 mg/kg iv (Ketavet), midazolam 0.5 mg/kg iv (Dormicum), and pancuronium bromide 0.2 mg/kg iv (Pancuronium Organon; Organon, Germany), the trachea was intubated (Super Safety Clear 6.0 mm ID; Rüsch, Germany), and a volume-controlled ventilation (Fabius Tiro; Dräger, Germany) was performed with a tidal volume of 10 ml/kg and a ventilation frequency of 14 to 18 per min to maintain an end-tidal carbon dioxide concentration of 35 to 40 mmHg. The inspiratory oxygen concentration was set to 30%. During the instrumentation and stabilization period, anesthesia was started with propofol at 20 mg · kg^{-1} · h^{-1} iv (Disoprivan 2; AstraZeneca, Germany) and remifentanil at 50 μg · kg^{-1} · h^{-1} iv (Ultiva; GlaxoSmithKline, Germany) using standard infusion pumps (Orchestra module DPS; Fresenius Kabi, Germany). During this time period, the infusion rates were manually adapted to maintain adequate anesthesia and to avoid large variation in heart rate and arterial blood pressure, as soon as these variables were available. All animals received 2 g of cefotaxim sodium (Cefotaxim, Germany) as short infusion before the instrumentation procedure.

After surgical exposure, the right femoral artery was cannulated and a PiCCO catheter was inserted by Seldinger technique and connected to a PiCCO plus monitor (Pulsion Medical Systems, Germany) for continuous monitoring of arterial pressure. A 6.0F introducer (Arrow; Teleflex Medical, Germany) and a 9.0F introducer (Edwards Lifesciences Services, Germany) were inserted with ultrasound guidance into the right jugular vein. Through the 9.0F introducer, a Swan–Ganz catheter (Edwards Lifesciences Services, Germany) was advanced *via* superior vena cava and cardiac chambers and placed in the pulmonary artery under continuous visual inspection of the transduced pressure curve. The pulmonary arterial catheter was connected to a Vigilance II monitor (Edwards Lifesciences Services) for continuous measurement of CO and body temperature. To provide the option of ventricular pacing, a 5.0F bipolar temporary pacing balloon catheter (Arrow; Teleflex Medical, Germany) was advanced through the 6.0F introducer *via* the superior vena cava and placed in the right ventricle. The left jugular vein was cannulated with a central venous catheter (Arrow 5-lumen catheter; Teleflex Medical, Ireland) by ultrasound-guided Seldinger technique. The urinary bladder was cathetered through a midline mini laparotomy (Cystofix; B. Braun, Germany). Baseline CO, heart rate, and mean arterial pressure were measured before starting the experimental intervention protocol during a 30-min procedure-free stabilization period.

Experimental Protocol

Provided a stable CO baseline, the animals received either continuous infusion of Ringer's solution, esmolol (Brevibloc; Baxter, Germany) or dobutamine (Dobutrex; Eli Lilly, Austria) according to the randomization to control, low CO, and high CO group, respectively. In the CO intervention groups, the esmolol and dobutamine infusions were manually titrated to achieve and maintain CO values lower or higher than 40% from baseline, respectively. For maintaining the CO less than 40% from baseline, a titrated continuous infusion of the veterinary β-blocking agent carazolol (Suacron; Divasa-Farmavic, Spain) was allowed to enhance the esmolol effect if necessary. In the control group, Ringer's solution was started with 10 ml · kg^{-1} · h^{-1}, and it was manually adapted to maintain the CO within 10% from baseline values. The intended CO was maintained throughout the complete blood sampling period of the study. In each group, 5 min after achieving the intended CO value, remifentanil infusion was stopped, and after a further 5 min, a bolus of sufentanil citrate (Sufenta; Janssen-Cilag, Germany) of 0.5 μg/kg was administered, followed by a continuous infusion of 2.0 μg · kg^{-1} · h^{-1} for 120 min.

Hemodynamic Value Assessment

Digitized measurements of invasive arterial blood pressure, arterial oxygen saturation, body temperature, and CO were transferred from the monitoring devices to a laptop computer *via* serial interfaces and recorded on the hard disc for further offline analysis.

Blood Sampling

For blood gas analysis and for the measurement of the sufentanil concentration, 23 timed blood samples of 5 ml each were drawn from an arterial line into ethylenediaminetetraacetic acid–containing tubes (S-Monovette potassium EDTA; Sarstedt, Germany). Two blank samples[11] were drawn after the end of the instrumentation and shortly before start of the sufentanil infusion. Further samples were drawn 0.5, 1, 1.5,

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2, 3, 5, 7, 10, 30, 60, 90, and 120 min after start of the sufentanil infusion and 1, 5, 7, 10, 15, 30, 45, 60, and 90 min after stop of the sufentanil infusion. After each sample, the arterial catheter was flushed with 1 ml of heparinized NaCl solution. The samples were kept on ice, and plasma was separated within 15 min and stored at −70°C until analysis.

Sufentanil Drug Analysis

Total plasma concentrations of sufentanil were determined using a validated liquid chromatography–tandem mass spectrometric method as previously described.[12] The lower limit of quantification was 0.005 ng/ml. The coefficients of variation at sufentanil concentrations of 0.005, 0.25, and 2.5 ng/ml were 10.1, 4.0, and 6.3% for interday and 4.1, 3.4, and 1.2% for intraday variation, respectively.

Pharmacokinetic Analysis

The sufentanil concentrations were analyzed by nonlinear mixed-effect modeling using NONMEM (version 7.3.0; ICON Development Solutions, USA). The first-order conditional estimation method with interaction was used throughout the analysis. Interindividual variability was assumed to follow a log-normal distribution. Pharmacokinetic modeling was performed sequentially: A basic structural model was determined first fitting two- and three-compartment models with first-order elimination to the data. Estimated parameters were volumes of distribution and elimination and intercompartmental clearances. The individual Bayesian estimates of the pharmacokinetic parameters were plotted independently against the weight and against the individual median value of the CO. Linear regression analysis was used as a first test for covariate effects. Subsequently, selected covariates were incorporated to the basic structural model using linear relationships with centering on the median value of the covariate (*COV*) within the population:

$$\theta_{POP} = \theta_{TV} \cdot \left(1 + \theta_{COV} \cdot \frac{COV - Median(COV)}{Median(COV)}\right)$$

in which θ_{TV} is the typical value of the parameter, and θ_{COV} quantifies the covariate effect. Covariate effects were tested with the likelihood ratio test by stepwise forward inclusion and backward elimination of the covariate parameter. Prediction errors (PE) were determined for individual and population predictions, and model performance was assessed by the median prediction error = median(PE_{ij}) and the median absolute prediction error = median($|PE_{ij}|$). To test the predictive value of the final model on data that were not used for model building, we also performed a cross-validation.[13] Details of the pharmacokinetic modeling are given in the Supplemental Digital Content (http://links.lww.com/ALN/B669).

Simulations

Using the estimated parameters from the final pharmacokinetic model for the plasma concentrations of sufentanil, we performed several simulations to evaluate the pharmacokinetic findings. To show how CO influences dosing, we calculated the infusion rates necessary to maintain a defined target plasma concentration, as well as the cumulative doses associated with these infusion rates. Further, we computed the time needed for 25, 50, and 75% decreases in plasma concentration after continuous infusion (context-sensitive decrement times) for different CO values. Simulations were performed with R (version 3.2.2)[14] using RStudio (version 0.98.501).[15]

Statistical Analysis

The intersubject variability of CO measurements in populations of anesthetized pigs as expressed by the coefficient of variation, *i.e.*, the SD divided by the mean, varies in literature between 10 and 22% at rest and around 40% during sepsis.[4,16] Further, a 40% difference in CO between treatment and control group has been shown to significantly influence the elimination clearance of alfentanil in a pig circulatory model.[4] In our investigation, we intended to identify a 40% difference in CO means between treatment and control group for a maximum intersubject CO variability of 30%.

The sample size needed to identify a percentage change $PC = (\mu_1 - \mu_0)/\mu_0$ between two population means μ_0 and μ_1, for a two-sample two-sided test is[17]:

$$n = \frac{2 \cdot \left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 CV^2}{\left[\ln(1 - PC)\right]^2}$$

where CV is the coefficient of variation $\left(CV = \mu_0/\sigma_0 = \mu_1/\sigma_1\right)$. For PC = 40% and CV = 30%, at least six animals per group are required to reject the null hypothesis of no difference between means of treatment and control group with a power of 80% and a type I error probability of 5%. Assuming a dropout rate of 30%, a total of 24 animals had to be included in the study.

Biometric data were tested for differences between control and treatment group by a two-sample *t* test for independent groups. If data were not normally distributed, as assessed by the Shapiro–Wilk test, or had unequal variances, as assessed by the Levene test, the two-sample Mann–Whitney test was used as nonparametric alternative to the *t* test. The measured values for heart rate, mean arterial pressure, CO, and concentrations of sufentanil were analyzed by a generalized linear model for repeated measurements with the factors "group" (*i.e.*, control, low, and high CO) and "sample time" followed by Dunett's one-tailed *post hoc t* test between control and each treatment group.

The data are presented as means ± SD or as median and range if not stated otherwise. Statistical analysis was performed with SPSS (version 21.0.02; IBM SPSS Statistics, USA) and R (version 3.2.2)[14] using RStudio (version 0.98.501).[15]

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Results

From the 24 pigs enrolled in the study, 20 animals could be analyzed. One animal could not be successfully hemodynamically monitored, two animals developed electromechanical dissociation, and one animal developed sustained ventricular arrhythmia with unsuccessful defibrillation. Therefore, data from seven animals in the low, seven animals in the control, and six animals in the high CO group were included into further analysis.

Explorative Data Analysis

The average intrasubject coefficient of variation for CO, heart rate, and mean arterial pressure during the treatment time period of the study was 10.2 ± 4.0, 8.2 ± 2.7, and 11.5 ± 3.7%, respectively. Because these values were within accepted measurement variation of physiologic variables during steady-state conditions[18] and their time resolution was in seconds, we selected one value of CO, heart rate, and mean arterial pressure as the nearest time neighbor of each blood sample for further analysis. Table 1 summarizes the biometric and hemodynamic data. Figure 1 shows the time course of CO, heart rate, and mean arterial pressure.

The animals in the low CO group received carazolol at 2.4 (1.2 to 4.8) mg · kg^{-1} · h^{-1} in addition to esmolol 21.6 (12 to 30) mg · kg^{-1} · h^{-1}. The mean CO in this group was 46.3% lower than in the control group ($P < 0.001$). In the high CO group, the animals received dobutamine at 42 (24 to 90) μg · kg^{-1} · h^{-1}. The mean CO in this group was 77.8% higher than in the control group ($P < 0.001$).

The sufentanil administration lasted 120 (112 to 151) min, and the total sufentanil dose was 170 (141 to 225) μg. In two control animals, the sufentanil infusion was prolonged for technical reasons. In one animal from the low CO group, the experiment was ended prematurely, so that we could collect only 13 blood samples. In another animal, the last two blood samples at 60 and 90 min after stop of the sufentanil infusion showed an increase in measured plasma concentrations of 177 and 163%, respectively, when compared to the preceding one at 30 min after stop of sufentanil infusion, so they were considered to be outliers and removed from the data set. Therefore, pharmacokinetic analysis was based on 408 samples of measured concentrations (excluding the two blank samples in each animal before start of sufentanil administration). There were no concentrations below the lower limit of quantitation.

The initial plasma concentrations, *i.e.,* concentrations measured at 0.5 min after administration of the sufentanil bolus, were 6.7 (6.5 to 8.7) ng/ml, 2.8 (1.8 to 3.8) ng/ml, and 0.9 (0.7 to 2.4) ng/ml in the low, control, and high CO group, respectively ($P < 0.001$ for higher concentrations in low CO group and for lower concentrations in high CO group when compared to control group). The plasma concentrations during sufentanil infusion were 1.2 (0.3 to 8.7) ng/ml, 1.0 (0.3 to 3.8) ng/ml, and 0.5 (0.2 to 2.4) ng/ml in the low, control, and high CO group, respectively ($P < 0.001$ for differences between groups, *post hoc* $P = 0.003$ for higher concentrations in low CO group, and *post hoc* $P = 0.035$ for lower concentrations in high CO group when compared to control group, respectively). The time course of sufentanil concentrations is depicted in figure 2.

Pharmacokinetic Modeling

A two-compartment model was identified as the best basic model. The linear regression analysis of the individual estimates showed a significant increase of all clearances and volumes with CO (fig. 3), whereas age and weight did not show any effect on pharmacokinetic parameters. We therefore included CO as covariate for all clearances and volumes of distribution, assuming a linear relationship:

$$CL_1 = \theta_1 \cdot \left(1 + \theta_5 \cdot \frac{CO - 5}{5}\right)$$

$$V_1 = \theta_2 \cdot \left(1 + \theta_6 \cdot \frac{CO - 5}{5}\right)$$

$$CL_2 = \theta_3 \cdot \left(1 + \theta_7 \cdot \frac{CO - 5}{5}\right)$$

$$V_2 = \theta_4 \cdot \left(1 + \theta_8 \cdot \frac{CO - 5}{5}\right)$$

where CO is the individual median value of CO in l/min. The interindividual variability (expressed as %CV) of CL_1, V_1, CL_2, and V_2 decreased from 33, 74, 112, and 54% for the basic model to 17, 40, 40, and 23% for the final model, respectively. The inclusion of CO as a covariate also led to a decrease of median prediction error and median absolute prediction error from 5.9 and 35% for the basic model to 3.9 and 21.2% for the final model, respectively. In the cross-validation for the basic model, the median values of median prediction error and median absolute prediction error in the test sets were 9.5 and 32.8%, respectively. In

Table 1. Age, Weight, Heart Rate, Mean Arterial Blood Pressure, and Cardiac Output in the Three Study Groups

CO	N	Age, weeks	Weight, kg	HR (CBL)/min (%)	MAP (CBL), mmHg (%)	CO (CBL), l/min (%)
Control	7	11.7 ± 1.1	39.9 ± 4.6	97.8 ± 14.5 (–2.9 ± 9.2)	79.6 ± 17.0 (–8.8 ± 10.6)	5.4 ± 0.7 (4.5 ± 10.1)
Low	7	11.3 ± 0.5	36.9 ± 3.0	81.3 ± 8.9 (–20.4 ± 7.2)*	65.6 ± 13.8 (–23.8 ± 22.2)*	2.9 ± 0.7 (–45.4 ± 8.2)*
High	6	11.3 ± 0.8	37.1 ± 1.9	142.6 ± 20.2 (44.9 ± 14.7)*	99.7 ± 14.3 (16.7 ± 17.1)*	9.6 ± 1.6 (82.1 ± 36.9)*

Data are reported as mean ± SD.

*$P < 0.001$ compared to the control group.

CBL = change from baseline; CO = cardiac output; HR = heart rate; MAP = mean arterial pressure.

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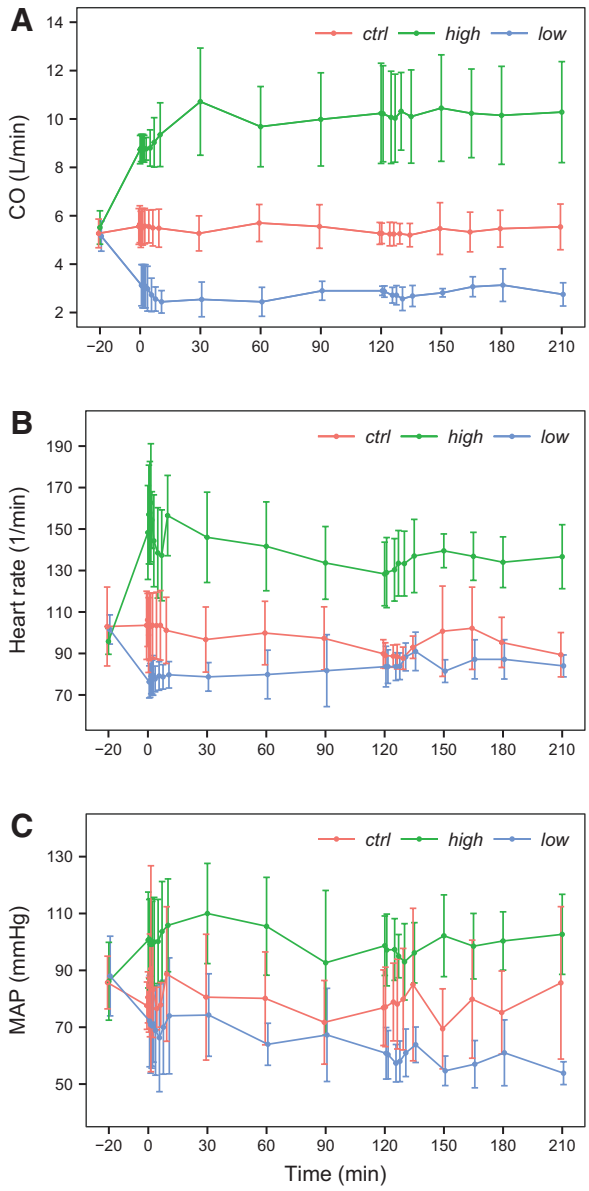

Fig. 1. Means ± SD of cardiac output (*A*), heart rate (*B*), and mean arterial pressure (*C*) in the three groups: control cardiac output group (ctrl), low cardiac output group (low), and high cardiac output group (high). CO = cardiac output; MAP = mean arterial pressure.

the cross-validation for the final model, the median values of median prediction error and median absolute prediction error in the test sets decreased to 7.8 and 22.9%, respectively. Table 2 summarizes the results for the final pharmacokinetic model for plasma concentrations of sufentanil. Median and 95% CIs of the bootstrap distributions showed a good agreement between population and bootstrap parameters.

Simulations

Figure 4 depicts the sufentanil infusion rate needed to maintain a constant sufentanil plasma concentration of 0.5 ng/ml for 3 h in three different CO groups: 3, 5, and 7 l/min. The

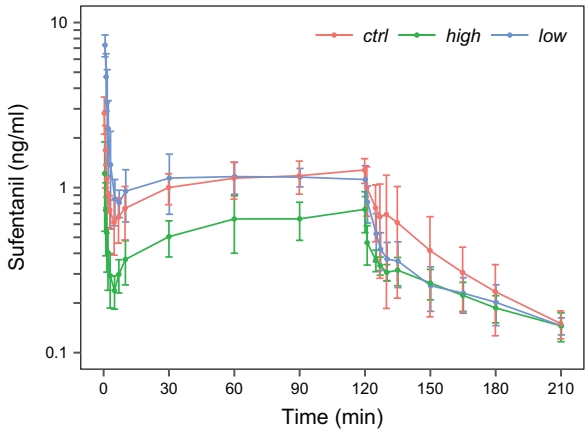

Fig. 2. Means ± SD of measured plasma concentrations of sufentanil in the three groups: control cardiac output group (ctrl), low cardiac output group (low), and high cardiac output group (high).

calculated population pharmacokinetic parameters for these CO values are presented in table 3. The total doses, including the loading dose for these groups were 99.5, 128.6, and 157.6 μg, respectively, and the loading doses were 0.8, 1.3, and 1.9 μg, respectively. The infusion rates at steady state were 0.47, 0.58, and 0.70 μg/min for the CO of 3, 5, and 7 l/min, respectively.

Figure 5 shows the context-sensitive half-times and 25 and 75% decrement times[19] for continuous sufentanil infusions of different length for CO values of 3, 5, and 7 l/min. For these CO values, there is a large nonlinear increase in the context-sensitive half-times (table 3; fig. 5).

Discussion

Drug-induced changes in CO caused inversely related changes in sufentanil concentrations of anesthetized pigs. Compartmental pharmacokinetic analysis of sufentanil concentration–time curves showed a significant increase of all clearances and distribution volumes with CO. When compared with the basic pharmacokinetic model without covariates, the inclusion of CO into the final model decreased the interindividual variability of all pharmacokinetic parameters and improved the prediction of sufentanil concentrations.

The sufentanil dosing in this study with an initial dose of 0.5 μg/kg followed by a continuous infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was similar to clinically used dosing schemes for general anesthesia in man.[20] In the control group, the measured plasma concentrations of sufentanil corresponded to the reported concentration range for clinical anesthesia of 0.5 to 2 ng/ml.[21] These findings verify the choice of the circulatory pig model for the experimental design of the study. However, our pig control group showed a median CO of 5 l/min that is similar to the CO at rest in humans but higher than the baseline CO in anesthetized pigs of 3.5 l/min and 2.2 l/min reported by Kuipers *et al.*[4] and Boer *et al.*,[22] respectively. These differences may be explained by differences in pig race, age, weight, feeding, and experimental protocol between studies.

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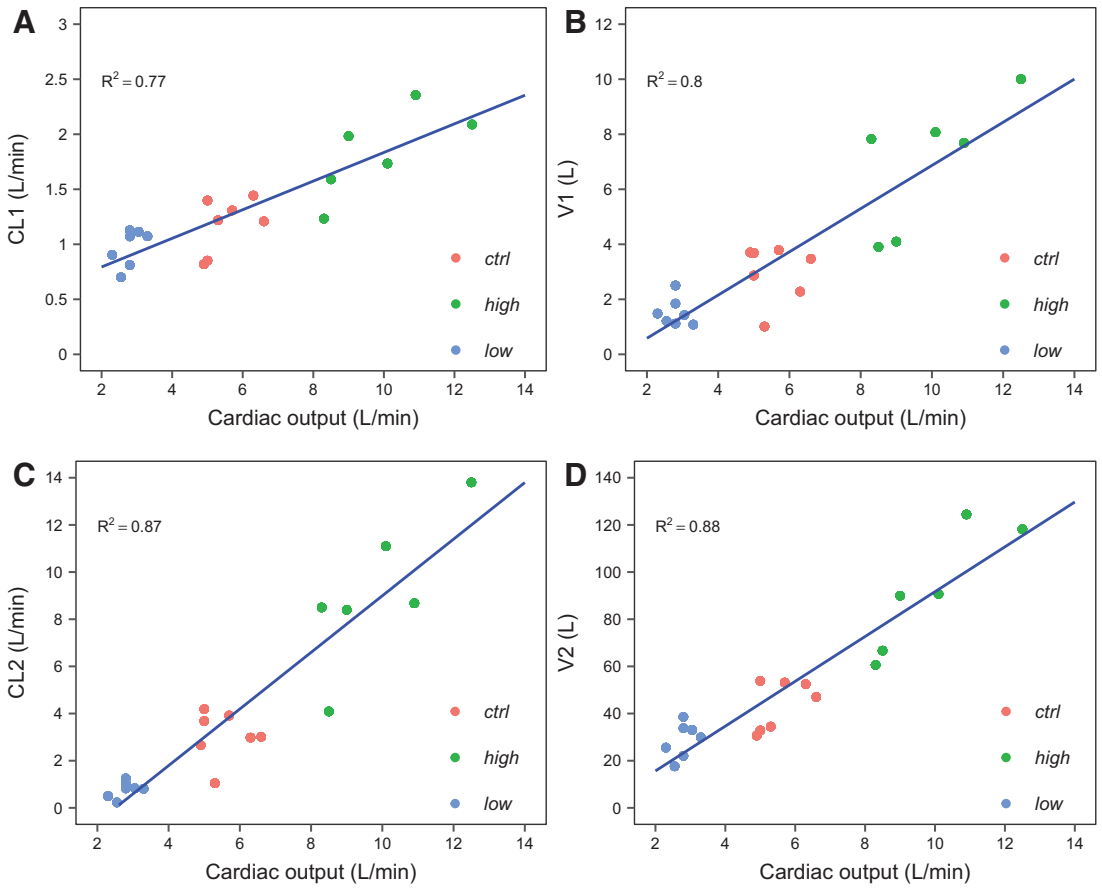

Fig. 3. Linear regression plots of the individual Bayesian pharmacokinetic parameters of sufentanil *versus* cardiac output. CL1 = elimination clearance; CL2 = distribution clearance; ctrl = control cardiac output group; high = high cardiac output group; low = low cardiac output group; R^2 = regression coefficient; V1 = central volume of distribution; V2 = peripheral volume of distribution.

Table 2. Pharmacokinetic Parameters of the Final Population Model for Sufentanil Concentrations

				Bootstrap Analysis	
Parameter	Model Relationship	Estimate	SEE	Median	95% CI
θ_1 (l/min)	$CL_1 = \theta_1 \cdot \left(1 + \theta_5 \cdot \frac{CO-5}{5}\right)$	1.17	0.05	1.18	1.07–1.29
θ_2 (l)	$V_1 = \theta_2 \cdot \left(1 + \theta_6 \cdot \frac{CO-5}{5}\right)$	2.69	0.49	2.78	1.78–3.76
θ_3 (l/min)	$CL_2 = \theta_3 \cdot \left(1 + \theta_7 \cdot \frac{CO-5}{5}\right)$	2.74	0.37	2.80	2.08–3.73
θ_4 (l)	$V_2 = \theta_4 \cdot \left(1 + \theta_8 \cdot \frac{CO-5}{5}\right)$	43.9	2.6	43.4	38.5–47.9
θ_5		0.49	0.07	0.48	0.36–0.60
θ_6		1.00	0.18	1.08	0.47–1.72
θ_7		1.64	0.07	1.64	1.48–1.99
θ_8		0.89	0.11	0.89	0.71–1.16
ω^2 CL_1		0.030	0.009	0.029	0.008–0.049
ω^2 V_1		0.163	0.077	0.158	0.026–0.362
ω^2 CL_2		0.161	0.051	0.152	0.051–0.323
ω^2 V_2		0.055	0.022	0.053	0.027–0.101
σ^2		0.045	0.006	0.043	0.034–0.053

CL_1 = elimination clearance; CL_2 = distribution clearance; SEE = standard error of the estimate; V_1 = central volume of distribution; V_2 = peripheral volume of distribution; σ^2 = intraindividual variance; ω^2 = interindividual variance.

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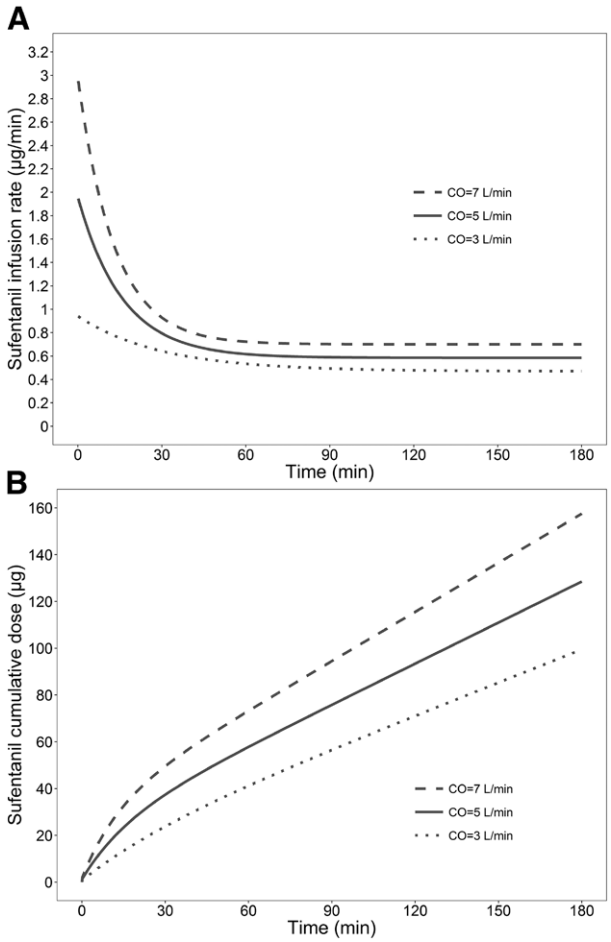

Fig. 4. Sufentanil infusion rate (*A*) required to maintain a constant total plasma concentration of sufentanil of 0.5 ng/ml for 3 h at three different cardiac output (CO) values of 3, 5, and 7 l/min, and sufentanil cumulative doses (*B*) associated with the infusions rates (*A*). Simulations were performed with the final model parameters (table 3).

Table 3. Effect of Cardiac Output on Typical Values of Pharmacokinetic Parameters

CO, l/min	3	5	7
CL_1, l/min	0.94	1.17	1.40
CL_2, l/min	0.94	2.74	4.54
V_1, l	1.61	2.69	3.77
V_2, l	28.21	43.80	59.39
V_{ss}, l	29.82	46.49	63.16
k_{10}, l/min	0.583	0.435	0.372
k_{12}, l/min	0.584	1.019	1.205
k_{21}, l/min	0.033	0.063	0.076
$T_{1/2,\alpha}$, min	0.59	0.46	0.42
$T_{1/2,\beta}$, min	42.13	38.15	39.92
A_{frac}	0.985	0.970	0.964
B_{frac}	0.015	0.030	0.036
$DT_{25\%,3h}$, min	0.6	1.2	2.6
$DT_{50\%,3h}$, min	3.1	19.9	25.7
$DT_{75\%,3h}$, min	43.8	58.1	65.6

A_{frac} = fractional coefficient of the α-term in the unit disposition function; B_{frac} = fractional coefficient of the β-term in the unit disposition function; CL_1 = elimination clearance; CL_2 = distribution clearance; CO = cardiac output; $DT_{25\text{-}75\%,3h}$, 25, 50, and 75% decrement time after 3 h of continuous infusion; k_{10} = elimination rate constant; k_{12} = transfer rate constant from central to peripheral compartment; k_{21} = transfer rate constant from peripheral to central compartment; $T_{1/2\ =\alpha}$ = fast distributional half-life; $T_{1/2=\beta}$ = terminal elimination half-life; V_1 = central volume of distribution; V_2 = peripheral volume of distribution; V_{ss} = volume of distribution at steady state.

In our study, increased or decreased CO was obtained by individual titration of dobutamine or β blockers to the intended CO condition, respectively. The CO was maintained stable in each animal throughout the blood sampling. Similar changes in CO could have been obtained by administering colloids or by withdrawing large amounts of blood but would have altered the initial volume of distribution and would not have maintained stable CO conditions. An alternate study design, in which CO is increased and decreased in each animal, would have probably resulted in a dropout rate of study animals higher than in our study because of an increased risk of complications, *e.g.,* malignant cardiac arrhythmias.

Altered CO may lead to hypo- and hyperdynamic circulatory states, as seen during clinical conditions with manifest heart failure or systemic inflammation, respectively. In our study, animals with low CO had sufentanil plasma concentrations that were significantly higher than those in animals of the control group. On the other hand, animals with high CO had concentrations significantly lower than those in animals of the control and low output cardiac group. The magnitude of this inverse relationship was more pronounced immediately after bolus administration than during continuous infusion (fig. 2).

The pharmacokinetic analysis identified a two-compartment model as the best basic model for sufentanil concentration–time curves. As depicted in figure 3, the individual pharmacokinetic estimates showed a significant increase of all volumes of distribution and clearances with CO. As expected, age and weight did not influence the pharmacokinetic estimates, because the variability of these potential pharmacokinetic covariates was low because of the animal selection and the feeding protocol before experiments. These findings indicate that CO influences the rate and the extent of tissue distribution, as well as the elimination clearance of sufentanil.

A possible limitation of our pharmacokinetic analysis may be the incorporation of CO as a single value per individual, *i.e.*, the individual median CO. However, because the CO was maintained stable throughout blood sampling time period and the intrasubject coefficient of variation for CO was within accepted measurement variation of physiologic variables during steady-state conditions, the predictive performance of the pharmacokinetic model would not change significantly.

The individual estimates of the elimination clearance increased linearly with increasing CO (fig. 3A), whereby

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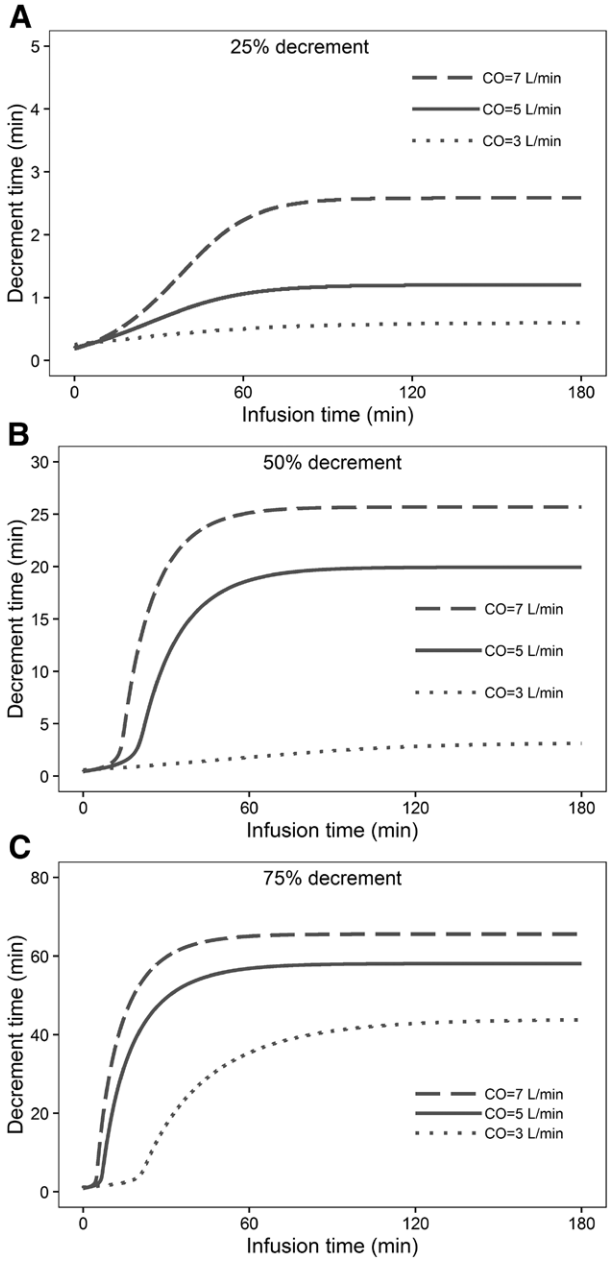

Fig. 5. Time required for 25% (*A*), 50% (*B*), and 75% (*C*) decrease in total plasma concentration of sufentanil after a continuous infusion of variable length at three different cardiac output (CO) values of 3, 5, and 7 l/min. Simulations were performed with the final model parameters (table 3).

the individual ratio of elimination clearance to CO was 24.9 ± 7.9% (mean ± SD). This linear relationship suggests a perfusion limited elimination of sufentanil. A similar relationship between elimination clearance and CO changes has been reported for single-dose administration of alfentanil and for short infusion of propofol in pig studies.[4,23]

The CO-induced changes in the sufentanil concentration *versus* time relationship may have clinical implications. Because both the volume of distribution and the elimination clearance increase with increased CO, sufentanil dosing should be related to the individual hemodynamic circulatory state. For clinical practice, the inclusion of CO in therapeutic algorithms may allow the dosing to be adjusted to the individual patient. As depicted in figure 4B, the total doses required for a dosing period of 3 h for a CO of 3 l/min would be approximately 38% lower than for a CO of 7 l/min.

To further evaluate the effect of CO on sufentanil pharmacokinetics, we estimated the time required for a 50% decrease in sufentanil plasma concentration after a continuous infusion of variable length (fig. 5). After 3 h of infusion, the simulated context-sensitive half time for a CO of 7 l/min was approximately eight times longer than for a CO of 3 l/min. This is surprising, because one may expect a more rapid decrease in plasma concentrations with increased drug clearance due to increased CO. However, this may apply when only clearance is altered and when pharmacokinetics can be described by a one-compartment pharmacokinetic model, where the elimination half-life can be a clinically useful indicator for dosing purposes. In this study, however, a two-compartment pharmacokinetic model described best the time course of sufentanil concentrations, and both clearances and volumes of distribution linearly increased with CO. Although the elimination half-life as well as the distributional half-life remained approximately constant with increasing CO, the context-sensitive time increased nonlinearly with increasing CO (table 3). This is caused by the decrease of the relative weight of the fast α-phase and the complementary increase of the relative weight of the slow β-phase with increasing CO, respectively (as described by A_{frac} and B_{frac} in table 3, which are the fractional coefficients of the α-term and β-term in the biexponential unit disposition function, respectively). In the context of a 3-h previous infusion, the decrement of concentration to 50% from baseline, *i.e.*, context-sensitive half-time, is mainly influenced by the α-phase in case of a CO of 3 l and by the β-phase in case of COs of 5 and 7 l (table 3). However, the magnitude of the nonlinear impact of cardiac output on context-sensitive decrement times is more pronounced in case of a 50% than in case of a 25% or 75% decrement time (fig. 5, A and C). These findings emphasize the important value of the context-sensitive half-time instead of the elimination half-life for the description of drug disposition for multicompartment pharmacokinetic models, where the distribution between central and peripheral compartments may be a relevant determinant of the time course of drug concentration in central compartment.

The importance of distributional processes for the sufentanil disposition is also evident when impaired CO returns to normal during recovery from anesthesia. Simulation results presented in the Supplemental Digital Content (figs. S5 to S8, http://links.lww.com/ALN/B669) suggest that an increase or decrease of CO after sufentanil infusion may increase the context-sensitive decrement times mainly caused by changes in the equilibration time between peripheral and central compartment.

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In conclusion, the results suggest that in case of an increased CO, it would be reasonable to increase the dose to avoid an inadequate drug effect, but one should also expect a longer recovery despite the increased CO. In case of a decreased CO, the dose should be reduced, and one may expect a faster recovery.

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Competing Interests

The authors declare no competing interests.

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