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EXPERIMENTAL

John A. Myburgh
Richard N. Upton
Cliff Grant
Allison Martinez

Epinephrine, norepinephrine and dopamine infusions decrease propofol concentrations during continuous propofol infusion in an ovine model

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J. A. Myburgh (✉) · R. N. Upton · C. Grant · A. Martinez
Department of Anaesthesia and Intensive Care, University of Adelaide, Royal Adelaide Hospital, Adelaide, Australia
E-mail: j.myburgh@unsw.edu.au
Phone: 61-2-93501111
Fax: 61-2-93503971

Address for correspondence: J. A. Myburgh, Department of Intensive Care, The St. George Hospital, Gray Street, Kogarah 2217, Sydney, Australia

Abstract *Objective*: To determine the effects of exogenous ramped infusions of epinephrine, norepinephrine and dopamine on arterial and effluent brain blood concentrations of propofol under steady state intravenous anesthesia.
Design: Prospective, randomized animal study.
Setting: University research laboratory.
Subjects: Five adult female merino sheep.
Interventions: Induction (5 mg/kg) and continuous infusion of propofol (15 mg/min) with controlled mechanical ventilation to maintain $PaCO_2$ 40 mmHg. After 1 h of continuous anesthesia, each animal randomly received ramped infusions of epinephrine, norepinephrine (10, 20, 40 μg/min) and dopamine (10, 20, 40 μg·kg·min) in 3 × 5 min intervals followed by a 30-min washout period.
Measurements: Arterial and sagittal sinus whole blood for determination of propofol concentrations using high-pressure liquid chromatography. Cardiac output using a thermodilution method. Level of consciousness using an observational scale.
Main results: All three drugs significantly and transiently increased cardiac output in a dose-dependent fashion to a maximum of 146–169 % of baseline. Baseline arterial and sagittal sinus propofol concentrations were not statistically different prior to catecholamine infusions. All three drugs significantly reduced mean arterial propofol concentrations (95 % CI, $p < 0.05$): epinephrine to 41.8 % of baseline (11.4–72), norepinephrine to 63 % (27–99) and dopamine to 52.9 % (18.5–87.3). There were parallel reductions of concentrations in sagittal sinus blood leaving the brain. The lowest blood concentrations were associated with emergence from anesthesia. Arterial concentrations were inversely related to the simultaneously determined cardiac output ($r^2 = 0.74$, $p < 0.0001$). Comparison of the data with the predictions of a previously developed recirculatory model of propofol disposition in sheep showed the data were consistent with a mechanism based on increased first pass dilution and clearance of propofol secondary to the increased cardiac output.
Conclusions: Catecholamines produced circulatory changes that reversed propofol anesthesia. These observations have potential clinical implications for the use of propofol in hyperdynamic circulatory conditions, either induced by exogenous catecholamine infusions or pathological states.

Key words Catecholamines · Propofol · Cardiac output · First pass dilution · Infusions · Clearance · Pharmacokinetics

Introduction

Augmentation of mean arterial pressure and cardiac output with infusions of catecholamines is a cornerstone of critical care medicine. However, relatively little attention has been given to the influence of the pharmacodynamic effects of exogenous catecholamines on the pharmacokinetics of other drugs. Clinical experience has shown that the pharmacokinetics of drugs used in critically ill patients may be markedly different from those in normal individuals, as reflected by the substantially different dose requirements in these patients. A number of mechanisms may be invoked, depending on the drug and disease state of the patient. These include altered clearance and volumes of distribution secondary to changes in tissue blood flow, metabolic activity, protein binding, pH and drug interactions [1, 2, 3, 4]. Catecholamines may influence pharmacokinetics by one or more of these mechanisms.

Recently, our laboratory conducted a series of experiments on the effect of increasing doses of catecholamines on cerebrovascular hemodynamics in an instrumented sheep preparation, anesthetized with a constant rate propofol infusion. As expected, higher doses of catecholamines were found to increase blood pressure and cardiac output [5]. However, it was also noticed that the times of the peak catecholamine dose were associated with the emergence of the sheep from propofol anesthesia. Given that both propofol and catecholamines are widely used in critical care medicine and the potentially important implications of such an interaction, we elected to quantitate this phenomenon in sheep as a first step in determining its mechanism and clinical significance.

Based on previous reports of an inverse relationship between cardiac output and propofol concentrations after short infusions [6], we hypothesized that this effect may also occur during longer propofol infusions when cardiac output was altered by catecholamine infusions. Our specific aims were, firstly, to document the effect of increasing doses of epinephrine, norepinephrine and dopamine on cardiac output, depth of anesthesia and the concentrations of propofol in arterial and effluent blood from the brain in instrumented sheep anesthetized with a constant rate propofol infusion. Secondly, to provide insight into the mechanisms involved; we wished to determine if a previously validated recirculatory model of propofol disposition in sheep [7, 8] could account for the observed changes in blood concentrations by altering the term for cardiac output in the model.

Materials and methods

Ethics statement

All experimental protocols were approved by the Animal Ethics Committee of the University of Adelaide. Care and handling of animals were in accordance with National Health and Medical Research Council guidelines.

Animal preparation

Female merino sheep of similar ages and body mass (40–50 kg) were used. Under halothane anesthesia, the animals were instrumented as described previously [9]. In summary, catheters were inserted into the descending aorta (for measurement of mean arterial pressure and sampling of arterial blood) and right atrium (for drug administration) via a femoral approach. A thermodilution cardiac output catheter was placed under pressure wave monitoring into the pulmonary artery. Via a craniotomy, a catheter was placed into the dorsal sagittal sinus which is the appropriate site for sampling cerebral venous blood in sheep [10].

Following this preparation, the sheep were recovered from anesthesia and housed in metabolic crates with free access to food and water [11]. A single dose of penicillin/streptomycin was administered perioperatively for antibiotic prophylaxis. Catheter patency was maintained by intraluminal heparin (10 IU/ml) locks.

Study design

At a later date, the sheep were re-anesthetized with propofol (5 mg/kg), endotracheally intubated and mechanically ventilated using a volume control ventilator (7000 Ventilator, Ohmeda, Madison, Wis., USA) to maintain an arterial carbon dioxide tension of 40 mmHg throughout the experiment. Anesthesia was maintained by continuous infusion of propofol at 15 mg/min throughout the protocol. Temperature and hydration were maintained throughout the experiment at baseline levels with external warming and intermittent infusions of saline according to central venous pressure, respectively. No muscle relaxant was used.

After 60 min of continuous intravenous anesthesia, pseudo-steady state was assumed based on previous studies and mathematical modeling of propofol disposition [12]. Thereafter, each animal received consecutive ramped infusions of epinephrine, norepinephrine or dopamine in random order. One hour elapsed between each catecholamine infusion to allow clearance of the preceding catecholamine and for measured parameters to return to baseline values. Each ramped infusion had three rates, each of 5 min duration, corresponding to 10, 20, and 40 μg/min for epinephrine and norepinephrine and 10, 20, 40 μg·kg·min for dopamine. Infusions were delivered in equivalent volumes so that milliliters/hour represented microgram/minute for epinephrine and norepinephrine and microgram/kilogram per minute for dopamine. At the end of the study, the sheep were recovered from anesthesia and returned to their metabolic crates.

Measurements and drug analysis

The following measurements were made at baseline, 5, 10, 15 min (during the catecholamine infusion) and 20, 25, 35 and 45 min (during washout). Arterial and sagittal sinus blood samples were taken for measurement of whole blood propofol concentrations and stored at –20 °C. They were subsequently assayed using a previously described method based on basic extraction and separation using a high pressure liquid chromatograph with fluorescence detection [9]. The limit of sensitivity was approximately 0.02 μg/ml. In each case, standard curves were prepared in blank blood taken immediately prior to the drug infusions with concentrations that spanned the expected concentration range. An assay was rejected

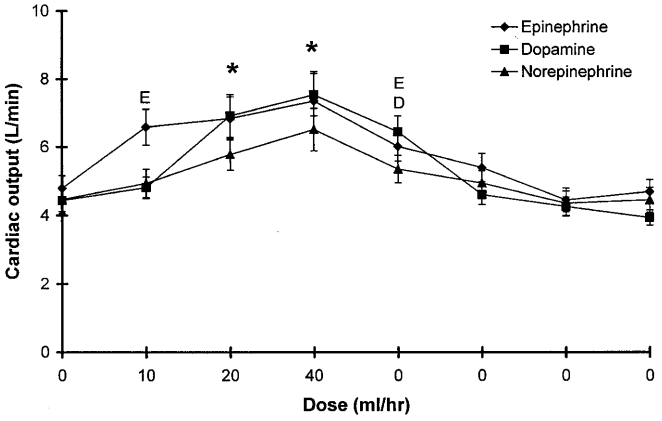

Fig. 1 The effect of catecholamine infusions on cardiac output (l/min) during continuous propofol anesthesia (15 mg/min). The x-axis represents the dose of catecholamine where milliliter/hour reflects microgram/minute concentrations for epinephrine and norepinephrine and microgram/kilogram per minute for dopamine. The data points correspond to measurements made at baseline, 5, 10, 15 min (during the catecholamine infusion) and 20, 25, 35 and 45 min (during washout), respectively. Values are expressed as mean ± SEM. Statistical significance was determined using 95 % confidence intervals, where $p < 0.05$ and is represented as an asterisk (*) for all three catecholamines and by *E* and *D* for epinephrine and dopamine, respectively

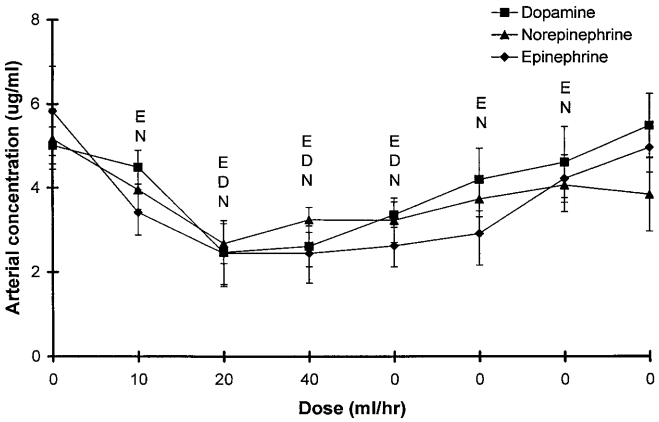

Fig. 2 The effect of catecholamine infusion on the mean concentrations of propofol in arterial blood (μg/ml) during continuous propofol anesthesia (15 mg/min). The x-axis represents the dose of catecholamine where milliliter/hour reflects microgram/minute concentrations for epinephrine and norepinephrine and microgram/kilogram per minute for dopamine. The data points correspond to measurements made at baseline, 5, 10, 15 min (during the catecholamine infusion) and 20, 25, 35 and 45 min (during washout), respectively. Values are expressed as mean ± SEM. Statistical significance was determined using 95 % confidence intervals, where $p < 0.05$ and is represented by *E*, *D* and *N* for epinephrine, dopamine and norepinephrine, respectively

if the r^2 value for linear regression of the standard curve was less than 0.995. The mean intra-assay coefficient of variation over the range 1.25–10 mg/l was 8.8 %. Cardiac output was measured using an intermittent thermodilution method with injections of iced saline (0–2 °C). Three injections were delivered throughout the respiratory cycle and values were rejected if there was more than 10 % deviation from the other values.

Qualitative, clinically based observations of the depth of anesthesia were expressed as a consciousness index. Assessments of the extent of (1) spontaneous limb or trunk movement and (2) the degree of swallowing or gagging on the endotracheal tube were made by giving each a score out of 3, where 0 represented no movement and 3 movement consistent with an awake animal. These two scores were summed to give the consciousness index, where a maximum of 6 corresponded to an awake animal and 0 represented complete anesthesia.

Comparison with model

A previously published recirculatory model of propofol disposition in sheep was used to simulate the experimental conditions [12]. This model has been extensively validated against in vivo data sets and differs from conventional compartmental models of propofol kinetics in that it accounts for the effect of both cardiac output and initial vascular mixing on initial drug concentrations. As for the experimental study, the propofol dose was set as a 250 mg intravenous bolus and an infusion of 15 mg/min for 240 min. In one simulation, the time-courses of the resultant arterial and sagittal sinus propofol concentrations were predicted assuming the cardiac output remained at the measured baseline value throughout the study. A second simulation was identical to the first except that cardiac output was transiently altered to the values measured during the periods of the catecholamine infusions. Due to restrictions imposed by the modeling software, these changes were assumed to be step changes that corresponded to the baseline and peak cardiac changes observed during the catecholamine infusions.

Statistical analysis

Comparison between groups was determined by the calculation of mean differences and 95 % confidence intervals assuming a *t*-distribution using the method described by Motulsky [13]. Two means were considered significantly different at the 95 % level if each of the means lay outside the confidence intervals of the other. Linear regression was performed using a spreadsheet program (Excel, Microsoft, USA).

Results

Five studies were performed in four sheep. The results are expressed as means (lower to upper 95 % confidence intervals). As expected, epinephrine, norepinephrine and dopamine increased cardiac output from baseline in a dose-dependent fashion, returning to baseline values within 30 min. Epinephrine increased mean cardiac output from 4.4 (3.5–5.4 CI) to 7.6 (5.6–9.1 CI) l/min, norepinephrine from 4.5 (3.6–5.3 CI) to 6.5 (5–8 CI) l/min and dopamine from 4.4 (3.5–5.4 CI) to 7.5 (5.9–9.1 CI) l/min (Fig. 1). The peak values were all statistically different from baseline by confidence interval analysis ($p < 0.05$).

Baseline mean arterial propofol concentrations were not statistically different prior to each catecholamine in-

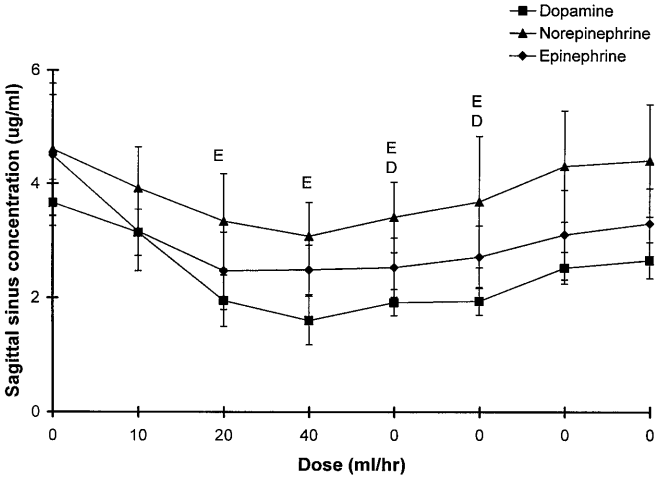

Fig. 3 The effect of catecholamine infusion on the mean concentrations of propofol in sagittal sinus blood (μg/ml) during continuous propofol anesthesia (15 mg/min). The x-axis represents the dose of catecholamine where milliliter/hour reflects microgram/minute concentrations for epinephrine and norepinephrine and microgram/kilogram per minute for dopamine. The data points correspond to measurements made at baseline, 5, 10, 15 minutes (during the catecholamine infusion) and 20, 25, 35 and 45 minutes (during washout), respectively. Values are expressed as mean ± SEM. Statistical significance was determined using 95% confidence intervals, where $p < 0.05$ and is represented by *E* and *D* for epinephrine and dopamine, respectively

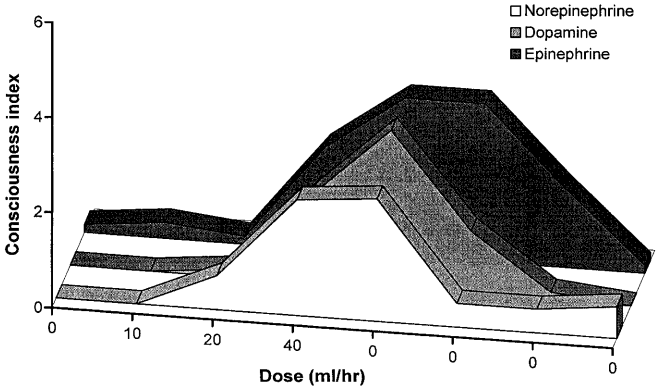

Fig. 4 Schematic diagram demonstrating level of consciousness index during infusions of catecholamines during continuous propofol anesthesia (15 mg/min). The scoring system is described in the text: the minimum value is 0 and is consistent with deep anesthesia and no spontaneous movement; maximum value is 6 and consistent with an awake animal. The x-axis represents the dose of catecholamine where milliliter/hour reflects microgram/minute concentrations for epinephrine and norepinephrine and microgram/kilogram per minute for dopamine. The data points correspond to measurements made at baseline, 5, 10, 15 min (during the catecholamine infusion) and 20, 25, 35 and 45 min (during washout), respectively

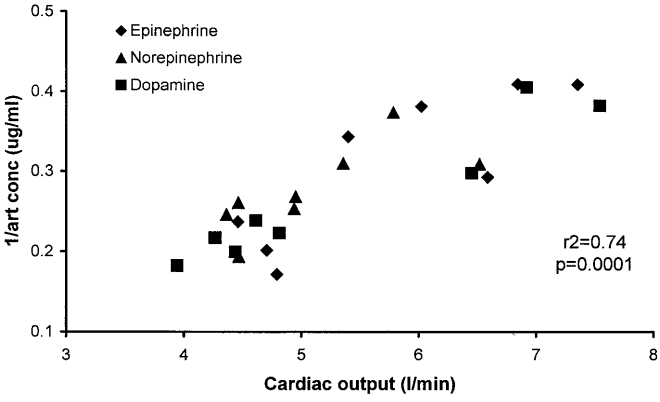

Fig. 5 Linear regression analysis of the inverse of arterial propofol concentration against the simultaneously measured cardiac output. Data points are the mean of five sheep, and represent measurements made during and after the catecholamine infusions

fusion (range 5.1–5.8 μg/ml). All three drugs significantly reduced mean arterial propofol concentrations from baseline (Fig. 2): epinephrine to 41.8% (11.4–72 CI), norepinephrine to 63% (27–99 CI) and dopamine to 52.9% (18.5–87.3 CI). There were parallel reductions in mean sagittal sinus propofol concentrations from a baseline concentration range of 2.6–4.6 μg/ml: epinephrine to 59.6% (39–80 CI) and norepinephrine to 70% (50–90 CI), which were significant reductions from baseline ($p < 0.05$), whilst reductions that occurred during dopamine to 48% (4–123 CI) did not achieve statistical significance ($p > 0.05$). (Fig. 3).

Lowest blood concentrations were associated with emergence from anesthesia, measured with the observational score (Fig. 4). The pattern of emergence from anesthesia was similar for all three catecholamines, beginning during the mid range of the infusions (20 μg/min for epinephrine and norepinephrine, 20 μg·kg·min for dopamine), reaching a maximum in the 5-min period after cessation of infusion and returning to baseline anesthesia levels within 20 min after cessation.

As the expected relationship between cardiac output and arterial propofol concentration is inverse [6], linear regression analysis between the two parameters was determined by using the inverse of arterial propofol concentration, yielding a r^2 value of 0.74 (Fig. 5).

The model simulations showed that the concentration changes observed were broadly consistent with the predictions of the model when cardiac output was changed (Fig. 6). The predicted baseline concentrations were slightly less than those observed, presumably due to some physiological difference between the present sheep and those used to define the model, but the predicted concentrations showed reductions during the catecholamine infusions that were within the 95% confidence intervals of the observed data (Fig. 6).

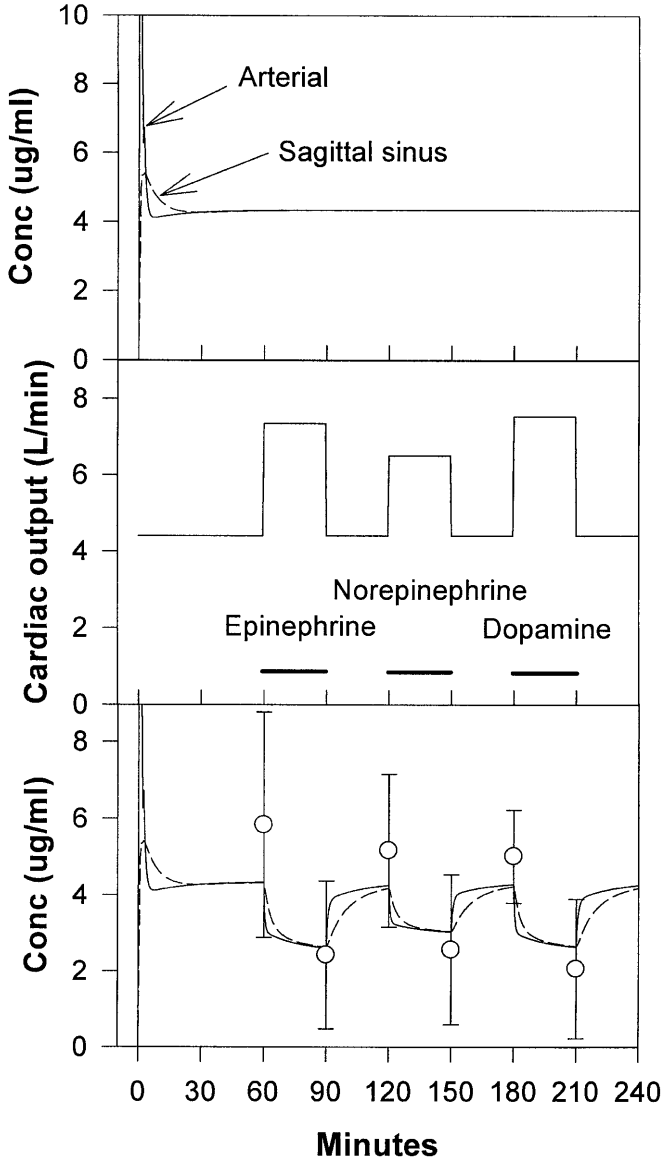

Fig. 6 An investigation of mechanisms underlying the observed concentration changes using a recirculatory pharmacokinetic model of propofol disposition in sheep. Upper panel: The predictions of the model when propofol was administered as a 250 mg bolus followed by a 15 mg/min infusion and cardiac output was a constant value of 4.4 l/min. Both the arterial and sagittal sinus concentrations rapidly reached steady state. Middle panel: The time-course of cardiac output changes entered into the model that corresponded with the experimental measurements. Lower panel: The predicted time-course of the arterial and sagittal sinus concentrations when cardiac output was altered. The observed baseline and trough values for each catecholamine are shown as symbols (mean and 95 % confidence intervals). The predictions of the model were in broad agreement with the observed data, and lay within its 95 % confidence intervals. It can be concluded that the observed concentration changes are consistent with an explanation based on the kinetic changes secondary to the altered cardiac output produced by the catecholamines

Discussion

This study analyzed the effect of exogenous catecholamine infusions on the arterial and brain effluent concentrations of propofol during continuous propofol anesthesia. As expected, epinephrine, norepinephrine and dopamine induced an equivalent, dose-dependent hyperdynamic circulatory state secondary to initial and subsequent adrenergic stimulation [14]. The data supported the hypothesis that the increased cardiac output and hyperdynamic circulation produced by catecholamines altered the pharmacokinetics of propofol. This phenomenon is not catecholamine-induced tachyphylaxis, as the emergence from anesthesia was associated with significantly lower blood concentrations of propofol in arterial blood and blood emerging from the brain. Although there have been few kinetic studies in which cardiac output has been changed experimentally, a study in which nitroglycerin was infused in rats has reported data generally consistent with the present data [15].

The mechanisms underlying this phenomenon are complex and require different concepts to those inherent in traditional compartmental models of drug disposition [16]. These two- or three-compartment models are generally defined in terms of abstract rate constants rather than anatomically identifiable blood flows or organ volumes. In particular, the drug is added to a central distribution volume rather than a circulating flow of blood, which prevents such models accounting for cardiac output in a physiologically realistic manner. Consequently, a significant deficiency of these models, particularly with their application to critically ill patients, is their inability to predict the kinetic outcome of altered cardiac output and other circulatory changes. While drug clearance in such models can be made proportional to cardiac output, this is not the sole mechanism of the observed phenomenon. For this situation, a change in clearance output would require approximately five half-lives before a new steady state were achieved – this is not consistent with the rapid change in blood concentrations with altered cardiac output shown in Fig. 2. By a similar argument, an effect of catecholamines on the binding or distribution volumes of propofol would not account for the observed rapid changes in propofol blood concentrations. Furthermore, similar changes have been observed when cardiac output is changed by other means [6].

These deficiencies are addressed in physiological models that have an underlying recirculatory structure. Such models, in their minimal form, divide the body into pulmonary and systemic subsystems through which blood flows in a recirculatory manner at a rate given by the cardiac output. An intravenous infusion is therefore made into a flowing stream of venous blood that is diluted with the entire cardiac output by the time the right heart and pulmonary artery are reached. Recirculatory

models often predict a marked dependence of pharmacokinetics on cardiac output [7, 17, 18, 19]. Two mechanisms are thought to be involved [6]. Firstly, there is a direct indicator dilution effect between the venous drug injection site and arterial blood (i.e. across the pulmonary subsystem). This is analogous to the indicator principle used in thermodilution cardiac output measurement – a fixed dose added to a higher cardiac output will result in less drug or indicator per unit blood volume, and therefore lower concentrations. Indeed, the contribution of the first pass dilution effect (e.g. dose rate over cardiac output) to the total steady state arterial drug concentration (e.g. dose rate over clearance) will simply be the drug clearance over the cardiac output. This effect is therefore most significant for drugs with a high clearance [16]. For propofol, if the cardiac output is 5 l/min and the clearance is 2 l/min, the contribution of the first pass concentrations to the total steady state arterial concentration is approximately 20 %.

Secondly, higher cardiac outputs imply higher blood flows to the organs of drug elimination and distribution in the systemic subsystem which, for some drugs, increases the rate of their clearance and distribution resulting in lower recirculated concentrations. Taken together, both mechanisms imply higher cardiac outputs are associated with lower arterial concentrations after both intravenous bolus and infusion administration regimens. Both mechanisms are inherent in the model used for simulations in the present study.

We have previously documented an inverse relationship between cardiac output and the peak arterial concentrations of propofol after 2-min intravenous infusions in an instrumented sheep preparation [6]. This was attributed principally to the first mechanism and was considered of most importance after intravenous bolus injection of propofol, as used for the induction of anesthesia. The present data and the model simulations imply that changes in cardiac output could alter the concentrations of propofol during a constant rate infusion by both the first and second mechanisms acting in series. The general agreement between the model and the data in Fig. 6 suggests that the contribution of other mechanisms to the altered kinetics of propofol (e.g. catecholamine induced increases in hepatic and pulmonary extraction of propofol) are likely to be minor.

An important issue is the extent to which this phenomenon could be expected to occur in man. A feature of propofol disposition in sheep is non-linear metabolism in the lungs [7]. It is possible that this non-linearity contributes to the observed reduction in arterial concentration, as lung clearance will increase further as the arterial concentrations become lower. To examine this issue, the model was used to simulate the expected steady state arterial propofol concentrations for an infusion rate of 15 mg/min when the cardiac output was 4, 6 and 8 l/min, respectively. In the presence of non-linear lung metabolism of propofol, the concentrations were 4.7, 3.2 and 2.4 μg/ml, respectively. If no lung metabolism is assumed, these concentrations were 6.8, 5.5 and 4.9 μg/ml, respectively. The total reduction in concentration was therefore 50 % with lung metabolism and 28 % without – thus approximately half of the observed cardiac output dependence can be attributed to the known lung metabolism of propofol in sheep. With respect to man, there is limited information regarding its linearity and extent of lung clearance. However, it is known that propofol clearance apparently exceeds liver blood flow [20] and metabolism of propofol can occur in the absence of a liver [21]. There is some evidence for non-linearity as shown by non-linear increases in blood concentration with infusion rate [22] and progressive decreases in clearance with higher doses [23]. While this is circumstantial evidence for lung metabolism of propofol in man, if there is no such metabolism the extent of cardiac output dependence would be predicted to be approximately half that observed in sheep.

In conclusion, this study highlights an important pharmacokinetic interaction between exogenous catecholamine infusions and propofol, where an induced hyperdynamic circulatory state increased propofol requirements. As propofol is increasingly being used as a sole agent for the sedation of critically ill patients, associated hyperdynamic conditions, either drug-induced or secondary to pathological states such as sepsis, may increase the doses of propofol required. This phenomenon requires investigation in man with some urgency.

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