Mechanism-based pharmacodynamic model for propofol haemodynamic effects in healthy volunteers

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Abstract

**Background:** The adverse haemodynamic effects of the intravenous anaesthetic propofol are well known, yet few empirical models have explored the dose–response relationship. Evidence suggests that hypotension during general anaesthesia is associated with postoperative mortality. We developed a mechanism-based model that quantitatively characterises the magnitude of propofol-induced haemodynamic effects during general anaesthesia.

**Methods:** Mean arterial pressure (MAP), heart rate (HR) and pulse pressure (PP) measurements were available from 36 healthy volunteers who received propofol in a step-up and step-down fashion by target-controlled infusion using the Schnider pharmacokinetic model. A mechanistic pharmacodynamic model was explored based on the Snelder model. To benchmark the performance of this model, we developed empirical models for MAP, HR, and PP.

**Results:** The mechanistic model consisted of three turnover equations representing total peripheral resistance (TPR), stroke volume (SV), and HR. Propofol-induced changes were implemented by $E_{\text{max}}$ models on the zero-order production rates of the turnover equations for TPR and SV. The estimated 50% effective concentrations for propofol-induced changes in TPR and SV were 2.96 and 0.34 $\mu g$ ml$^{-1}$, respectively. The goodness-of-fit for the mechanism-based model was indistinguishable from the empirical models. Simulations showed that predictions from the mechanism-based model were similar to previously published MAP and HR observations.

**Conclusions:** We developed a mechanism-based pharmacodynamic model for propofol-induced changes in MAP, TPR, SV, and HR as a potential approach for predicting haemodynamic alterations.

**Clinical trial registration:** NCT02043938

**Keywords:** haemodynamic effects; healthy volunteers; mechanism-based pharmacodynamic modelling; pharmacology; propofol

**Abbreviations:** Base$_{\text{HR}}$ baseline of HR; Base$_{\text{SV}}$ baseline of SV; Base$_{\text{TPR}}$ baseline of TPR; BMI body mass index; BSV between subject variability; CO cardiac output; C50 the concentrations that produce half of the maximal drug effect; $E_{\text{max}}$ the maximum drug effect; FB feedback; HR heart rate; HR$_{\text{SV}}$ the magnitude of the effect of HR on SV; MAP mean arterial pressure; PP pulse pressure; RUV residual unexplained variability; SV stroke volume; TPR total peripheral resistance

Editor’s key points

- Propofol has adverse haemodynamic effects, but there are few published pharmacokinetic pharmacodynamic models for its haemodynamic effects, all of which are empirical models.
- The authors developed a mechanism-based model for the haemodynamic effects of propofol in healthy volunteers.
Propofol, a positive modulator of $\gamma$-aminobutyric acid receptors, is one of the most commonly used drugs for sedation and anaesthesia in clinical practice. The hypnotic and analgesic effects of propofol and the dose–exposure–response relationship have been extensively studied through pharmacokinetic–pharmacodynamic (PK–PD) modelling.\(^1\) The effects of propofol on changes in haemodynamic variables has also been studied after target-controlled infusion in healthy volunteers and patients.\(^1\) The most pronounced propofol-induced haemodynamic effect is a decrease in sympathetic tone resulting in vasoconstriction and a decrease in total peripheral resistance (TPR), which leads to a decrease in mean arterial pressure (MAP).\(^2\)

There is considerable concern that intraoperative hypotension is associated with postoperative mortality.\(^7\) Although extensive descriptive knowledge on the association between exposure and the cardiovascular safety of propofol is available, only a few mathematical models have addressed changes in haemodynamic variables during propofol infusion in humans, and they all use empirical approaches\(^8\)–\(^10\) ignoring the complex interactions in the cardiovascular system.

In contrast to empirical models, mechanism-based PK–PD models can distinguish between drug-specific parameters, describing the interaction between the drug and biological system, and biological system-specific parameters describing the functioning of the biological system such as feedback mechanisms. Mechanism-based models have better extrapolation properties,\(^1\) and therefore better characterise propofol-induced haemodynamic-side-effects.

Snelder and colleagues\(^12,13\) have developed a PK–PD model in rats that integrates a quantitative description of the physiology of the cardiovascular system and the effect of cardiovascular drugs on the relationship between MAP, TPR, HR, and stroke volume (SV). This model has been extended by including heart contractility data in dogs,\(^14\) and recent models with similar structure perform reasonably well in humans.\(^15,16\)

We aimed to develop a mechanism-based PK–PD model that describes the relationship between cardiovascular variables and propofol plasma concentrations using the principles outlined by Snelder and colleagues.\(^1\) In addition, three empirical models for MAP, HR, and pulse pressure (PP) (serving as a surrogate of SV in this study) were developed to benchmark the performance of the mechanism-based model. Finally, we performed simulations for the final mechanism-based model predicting the expected haemodynamic changes according to US Food and Drug Administration-approved drug labelling regulations and replicated published studies to evaluate the model.

Methods

Study design

The data used in this analysis were recorded as part of standard vital signs monitoring for safety purposes in a previous four-period randomised sequence crossover study as described.\(^17\) Screening and inclusion methods were described by Kuizenga and colleagues\(^17\) as shown in Online Supplementary 1 Figure 1–1. The study was approved by the Institutional Review Board of the University Medical Center Groningen (NL43238.042.13) and was registered at ClinicalTrials.gov (NCT02043938). In brief, 36 healthy volunteers with ASA physical status 1 were enrolled. After written informed consent was obtained, volunteers were stratified by age and sex (Online Supplementary 2, Table 2–1). Each volunteer received an arterial line for blood sampling and an intravenous line for the administration of crystalloids (2 ml kg\(^{-1}\) h\(^{-1}\)). Propofol 2% (B. Braun, Melsungen, Germany) was administered via the same intravenous line using a Fresenius Base Primea docking station (Fresenius-Kabi, Bad Homburg, Germany) carrying two Fresenius Module DPS pumps. RUGLOOP II software (Demed, Temse, Belgium) was used to control infusion rates between 0 and 1200 ml h\(^{-1}\) via an RS-232 interface. After 2 min of baseline measurements, a ‘staircase’ step-up followed by step-down infusion of propofol was initiated. Effect-site concentration targets were set at 0.5, 1, 1.5, 2.5, 3.5, 4.5, 6, and 7.5 $\mu$g ml\(^{-1}\) using a three-compartment pharmacokinetic model with an effect compartment developed by Schneider and colleagues.\(^16,17\) Drug administration was stopped when burst suppression ratio by EEG reached 40%. At that point, propofol effect-site concentration targets were decreased with the inverse steps as performed during induction followed by a single bolus. Each target was maintained for 12 min to reach equilibrium, and arterial blood samples were taken at the end of the equilibration time as described.\(^17,20\)

Pharmacodynamic measurements and data handling

Each volunteer was connected to a Philips IntelliVue MP50 vital signs monitor (Philips Medizin Systeme, Boeblingen, Germany) for ECG and noninvasive blood pressure measurements. Noninvasive systolic and diastolic blood pressure were measured every minute. HR was derived from the ECG and was recorded every second. All variables were collected using RUGLOOP II software. Mean arterial blood pressure and PP were calculated from the measured systolic and diastolic blood pressure.

Because of the length of the study sessions, our dataset contained more than 10 000 combined observations for HR for each individual. To reduce the computational burden during model development, we reduced the number of HR measurements per subject. Before data reduction, we applied a median filter to reduce the influence of artifacts or outlying data. The width (span) of the median filter was 30 s. Data reduction was performed by retaining only the first out of every 60 consecutive median filtered observations in the dataset.

Population PK–PD modelling

The ‘individual pharmacokinetic parameter approach’ was applied to develop the PK–PD models.\(^15\) Plasma concentration measurements were used to derive individual post hoc pharmacokinetic parameters (CL, Q2, Q3, V1, V2, and V3) based on the propofol pharmacokinetic model published by Eleveld and
colleagues,\textsuperscript{1} and the pharmacokinetic parameters for each individual were fixed in the subsequent pharmacodynamic modelling. Goodness-of-fit plots for the Eleveld pharmacokinetic model for describing the propofol pharmacokinetics of this particular dataset is shown in Online Supplementary 3, Figs 3–1.

The model by Snelder and colleagues\textsuperscript{13} was used as a starting point for development of the mechanism-based model. This model assumes that MAP is the product of cardiac output (CO) and TPR and that CO is the product of HR and SV, as in equation (1).\textsuperscript{2,22–27} As SV and TPR were not measured directly, we used PP as a surrogate of SV, taking into account an SV/PP ratio of 1.5,\textsuperscript{23–25} and TPR was implemented as a latent variable in line with contemporary pharmacometric approaches for handling longitudinally correlated data.\textsuperscript{28} A latent variable is a variable that is not directly observed but its dynamics can be inferred (through the model) from other observable correlated variables (much like the hypothetical effect-site concentration that is used in effect-site PK–PD models).

\[
\text{MAP} = \text{CO} \times \text{TPR} = \text{HR} \times \text{SV} \times \text{TPR}
\]

The Snelder model consists of three turnover equations for TPR, SV, and HR and a negative feedback mechanism between these variables, through MAP, representing the homeostatic feedback of the baroreflex system. A direct inverse relationship between HR and SV was also included, representing the effect of shorter left ventricular filling time because of increased HR thereby decreasing SV (expressed as $HR \times SV$).\textsuperscript{13}

In line with the approach of Snelder and colleagues, we explored propofol effects on the turnover equations for TPR, SV, and HR. Propofol-induced increase or decrease in zero-order production rate constants ($k_{pu}$) or first-order dissipation rate constants ($k_{wd}$) of the turnover equations were explored using $E_{\text{max}}$ and sigmoid $E_{\text{max}}$ models. The parameter that describes the relationship between HR and SV (HR,SV) was fixed to the value reported by Snelder and colleagues.\textsuperscript{13} The focus of the development of the mechanism-based model was to construct a model with as few propofol drug effect parameters as possible, and with a goodness-of-fit comparable with the empirical models (as judged by goodness-of-fit plots and prediction-corrected visual predictive checks).

For the separate empirical pharmacodynamic models for MAP, HR, and SV, the hysteresis between predicted plasma concentrations and the pharmacodynamic measurements was described by an indirect response model.\textsuperscript{27} The concentration–effect relationships were explored using $E_{\text{max}}$ and sigmoid $E_{\text{max}}$ models.

As MAP and HR were elevated before propofol infusion, we explored whether including a time-dependent effect in the models could improve the goodness-of-fit. The effect was estimated by an empirical function with two parameters $k$ and LTDE; equations (2) and (3). TDE\textsubscript{0} represents the magnitude of the initial time-dependent effect. LTDE described the level of this effect influencing baseline MAP and baseline HR (expressed as percentage of increased baselines) with a first-order dissipation rate constant $k$. Base\textsubscript{HR} represents baseline HR.

\[
\text{TDE}_0 = \text{LTDE} \times \text{Base}_{\text{HR}}
\]

\[
\frac{d\text{TDE}}{dt} = - k \cdot \text{TDE}
\]

Once the basic model was established, the correlations between post hoc predicted parameters for which between-subject variability (BSV) was included and covariates were analysed. Subsequently, the influence of these covariates was evaluated by inclusion in the models. The inclusion of covariates was accepted only if the objective function value decreased more than 3.85 points, which is the 5% significance level critical quintile of the corresponding $\chi^2$ distribution. The covariates considered were age, weight, height, sex, and BMI.

**Parameter estimation and model evaluation**

The MAP, PP, and HR observations were simultaneously fitted using the first-order conditional estimation method with interaction using NONMEM (version 7.4; Icon Development Solutions, Hanover, MD, USA). BSV was modelled using exponential or additive models. Residual variability was described using additive error models, proportional error models, or both. At each step of model building, the change in objective function value and the median absolute population prediction error were compared between candidate models. Goodness-of-fit was graphically evaluated by plotting individual or population predictions vs the observations and the conditionally weighted residuals (CWRES) vs population predictions and time. Parameter uncertainty of the models was estimated using the covariance step in NONMEM or sampling importance resampling.\textsuperscript{29} Finally, prediction-corrected visual predictive checks were used to internally evaluate the models.\textsuperscript{30} All models and simulations were run using PsN\textsuperscript{28} and Pirana\textsuperscript{31} as back end, front end, or both to NONMEM. Graphical assessment of the goodness-of-fit and simulations and the construction of the prediction-corrected visual predictive checks were conducted in R (R Foundation for Statistical Computing, Vienna, Austria).\textsuperscript{31}

**Simulations for the mechanism-based model**

The final mechanism-based PK–PD model was used to predict expected changes in haemodynamic variables during general anaesthesia for the dosing recommendations described in the propofol US Food and Drug Administration-approved drug label.\textsuperscript{25} According to the label, adults (<55 yr old) received an induction dose of 2.5 mg kg\textsuperscript{-1} and a maintenance dose of 0.2 mg kg\textsuperscript{-1} min\textsuperscript{-1} for the first 15 min followed by a reduction of 40% (0.12 mg kg\textsuperscript{-1} min\textsuperscript{-1}) up to 30 min followed by 0.1 mg kg\textsuperscript{-1} min\textsuperscript{-1} afterwards. For older individuals (>55 yr old), the induction dose was 1.5 mg kg\textsuperscript{-1} and maintenance 0.1 mg kg\textsuperscript{-1} min\textsuperscript{-1}. For the simulations, the distribution of covariates (age, weight, and sex) was according to the covariate distribution (including correlations between covariates) in our study population. We also simulated propofol concentration–effect relationships for MAP, HR, and PP in a 35-yr-old individual.

We performed 1000 simulations to obtain 95% prediction intervals for MAP and HR to benchmark our model against the available literature. First, we replicated the study by Fairfield and colleagues,\textsuperscript{21} which consisted of nine patients with a mean age of 23 yr (95% confidence interval [CI], 20–26 yr) and mean weight of 67 kg (95% CI, 59–75 kg) who received an infusion of propofol 2.5 mg kg\textsuperscript{-1} i.v. for 20 s. We also simulated the study by Maneglia and Cousin,\textsuperscript{24} which focused on eight females with a mean age of 86 (standard error of the mean [SEM], 5.4) yr and mean weight of 51.8 kg, who received an induction dose of propofol 1 mg kg\textsuperscript{-1} and a maintenance infusion of 0.1 mg kg\textsuperscript{-1} min\textsuperscript{-1} i.v.
The Pharmacodynamic empirical models appeared to decrease only mildly during propofol infusion. The change in HR was similar, yet inverse to the change in MAP.

All volunteers received propofol according to a step-up and step-down target-controlled infusion. Propofol plasma concentrations, MAP, HR, and PP observations used for modelling are shown in Online Supplementary 4, Figs 4–1, which shows that MAP decreases in the step-up phase, then increases in the step-down phase and decreases again around the time of the bolus. The change in HR was similar, yet inverse to the change in MAP. PP appeared to decrease only mildly during propofol infusion.

### Statistical analysis

Model parameters are reported as typical values with associated relative standard errors (RSEs) derived from covariance matrix or sampling importance resampling.35

### Results

All volunteers received propofol according to a step-up and step-down target-controlled infusion. Propofol plasma concentrations, MAP, HR, and PP observations used for modelling are shown in Online Supplementary 4, Figs 4–1, which shows that MAP decreases in the step-up phase, then increases in the step-down phase and decreases again around the time of the bolus. The change in HR was similar, yet inverse to the change in MAP. PP appeared to decrease only mildly during propofol infusion.

### Pharmacodynamic empirical models

The \( E_{\text{max}} \) functions characterise the relationship between the predicted propofol plasma concentrations and MAP, HR, and PP. Estimated \( E_{\text{max}} \) values for MAP and HR were \( -40.0\% \) and \( 26.0\% \), respectively. For PP, the estimated maximum effect of PP \( (E_{\text{max,PP}}) \) was \( -8.9\% \) with individual estimates ranging from \( -116.8\% \) to \( 54.9\% \). We found that \( E_{\text{max,PP}} \) negatively correlated with baseline PP \( (\text{Base}_{\text{PP}}, p=-0.72) \), meaning that individuals with higher than typical baseline PP were more likely to have a lower than typical \( E_{\text{max,PP}} \) \( (\rho \) is the correlation coefficient). The estimated half-lives for the MAP, HR, and PP models were \( 3.15, 7.79, \) and \( 5.78 \) min, respectively, indicating that MAP changed first followed by PP and HR. The time-dependent effect in equations (2) and (3) was significant for MAP \( (\Delta \text{ objective function value}= -91.0) \) and HR \( (\Delta \text{ objective function value}= -16.9) \), and resulted in a temporary increase in MAP by 6 mm Hg and HR by 3 beats min\(^{-1} \) with a half-life for attenuation of 14.74 and 5.46 min, respectively. Age was a significant covariate on \( \text{Base}_{\text{MAP}} \) \( (\Delta \text{ objective function value}= -13.3) \) and \( E_{\text{max,PP}} \) \( (\Delta \text{ objective function value}= -15.2) \), with \( \text{Base}_{\text{MAP}} \) and \( E_{\text{max,PP}} \) increasing with age according to equations (4) and (5). \( \text{Base}_{\text{MAP}} \) (typ) and \( E_{\text{max,PP}} \) (typ) are the population typical values of baseline MAP and the maximal effect of propofol on PP. \( \eta_1 \) and \( \eta_2 \) are random variables representing BSV. No other covariates were significant.

\[
\text{Base}_{\text{MAP}} = \text{Base}_{\text{MAP}}\text{(typ)} \cdot e^{0.0039 \cdot (\text{AGE} - 35)} \cdot e^{\eta_1} \]  

\[
E_{\text{max,PP}} = E_{\text{max,PP}}\text{(typ)} \cdot e^{0.053 \cdot (\text{AGE} - 35)} + \eta_2 \]
three empirical models are shown in Online Supplementary 5, Figs 5–4,5–5, and 5–6, respectively. These figures show that the empirical models adequately describe propofol-induced changes in MAP, HR, and PP.

**Mechanism-based model**

Propofol plasma concentrations negatively affected the production rates of TPR (k_{in,TPR}) and SV (k_{in,SV}), which was best described using a sigmoid E_{max} model and an E_{max} model, respectively. Inclusion of an additional propofol effect on the turnover equation for HR did not improve the model. Initially, we estimated a separate k_{out} for each of the turnover equations for TPR, SV, and HR. However, these parameter estimates were on the same order of magnitude (0.078, 0.072, and 0.073 min^{-1} for TPR, SV, and HR, respectively). Therefore, one k_{out} was estimated instead (Δ objective function value = 1.8).

A time-dependent effect, as in equations (2) and (3), was significant for HR and accounted for the elevated HR before the start of the study session (Δ objective function value = -537.2). The BSV for the estimated baseline parameters for SV, HR, and TPR (BSV_{BaseSV}, BSV_{BaseHR}, and BSV_{BaseTPR}, respectively) were highly correlated. Inclusion of these correlations (denoted by pBase_{HR}, pBase_{TPR}, and pBase_{SV} in Table 1) in the stochastic model resulted in improvement in the model’s goodness-of-fit (Δ objective function value = -59.5) and prediction-corrected visual predictive checks. Residual errors on SV, HR, and TPR were described using additive residual error models.

The final mechanism-based model is shown in equations (6)–(11), and the structure of the model is graphically depicted in Fig 1. In these equations, C_p represents the plasma propofol concentration; k_{in,TPR}, k_{in,SV}, and k_{in,HR} represent the zero-order production rate constants and k_{out} is the first-order dissipation rate constant of TPR, SV, and HR. E_{max,TPR} and E_{max,SV} are the maximum effects of propofol on TPR and SV, respectively. EC_{50,TPR} and EC_{50,SV} are the concentrations that produce 50% of the maximal drug effect on TPR and SV, respectively. SV^* represents the SV affected by the negative change in MAP and drug effect. HR^* represents the HR influenced by the feedback of MAP. RMAP is MAP normalised to baseline values. FB is power of the negative feedback of MAP on TPR, SV, and HR, respectively. HR_{SV} is a constant that represents the magnitude of the direct inverse effect of HR on SV.

\[
\frac{dTPR}{dt} = k_{in,TPR} \cdot RMAP^{FB} \cdot \left(1 + \frac{E_{max,TPR} \cdot C_p^\gamma}{EC50_{TPR}^\gamma + C_p^\gamma}\right) - k_{out} \cdot TPR
\]  

(6)

\[
\frac{dSV^*}{dt} = k_{in,SV} \cdot RMAP^{FB} \cdot \left(1 - \frac{E_{max,SV} \cdot C_p}{EC50_{SV} + C_p}\right) - k_{out} \cdot SV^*
\]  

(7)

\[
\frac{dHR^*}{dt} = k_{in,HR} \cdot RMAP^{FB} - k_{out} \cdot HR^*
\]  

(8)

SV = SV^* \cdot \left[1 - HR_{SV} \cdot \ln\left(\frac{HR}{HR_{Base}}\right)\right]

\[
HR = HR^* + TDE
\]  

(9)

HR = HR^* + TDE

MAP = TPR \times HR \times SV

PP = SV/1.5

\[
SV = SV^* \cdot \left[1 - HR_{SV} \cdot \ln\left(\frac{HR}{HR_{Base}}\right)\right]
\]

MAP equals the product of TPR, HR, and SV. The influences of negative feedback through MAP on TPR, HR, and SV are represented by three linked turnover equations. Propofol decreases the zero-order production rates (k_in) of the turnover equations for TPR and SV. SV is influenced by the drug effect and negative feedback through MAP (SV^*) and by direct inverse relationship through HR (represented by HR_{SV}). HR is described by combination effects of time-dependent effect (which will cause a temporary increase in HR, expressed as TDE) and feedback from MAP (HR^*). PP is a surrogate of SV (taking into account an SV/PP ratio equals to 1.5). In this model, EFF_{TPR} and EFF_{SV} represent the drug effect on TPR and SV. k_{in,HR}, k_{in,SV}, and k_{in,TPR} are the zero-order production rate constants of HR, SV, and TPR, respectively. k_{out} is the first-order dissipation rate constant. FB is the power of the feedback on HR, SV and TPR. SV, stroke volume; TPR, total peripheral resistance; PP, pulse pressure.
RMAP = \frac{HR \cdot SV \cdot TPR}{Base_{HR} \cdot Base_{SV} \cdot Base_{TPR}} \quad (11)

Inclusion of age in the $E_{\text{max,SV}}$ resulted in a significant decrease in the model’s objective function value (~1381.8). $E_{\text{max,SV}}$ increased with age according to equation (12). $E_{\text{max,SV}(\text{typ})}$ is the population typical value of the maximal effect of propofol on SV. No other covariates were included in the final model.

$$E_{\text{max,SV}} = E_{\text{max,SV(\text{typ})}} \cdot e^{0.026 \cdot (\text{AGE} - 35)} \quad (12)$$

**Final mechanism-based model**

The estimated parameters and associated uncertainty in the estimates are shown in Table 1. According to the model, a typical individual has a baseline MAP of 76 mm Hg. This value is calculated from baseline SV, HR, and TPR according to equation (1). The estimated $k_{\text{out}}$ of SV, HR, and TPR was 0.075 min$^{-1}$ (half-life of 9.19 min). The time-dependent effect caused a temporary increase in HR by 10 beats min$^{-1}$ with a first order half-life of attenuation of 19.36 min. MAP changed accordingly and, in a typical individual, increased by 14 mm Hg. The individual estimate for baseline TPR ($Base_{TPR}$) negatively correlated with baseline SV ($Base_{SV}$, $p = -0.66$) and baseline HR ($Base_{HR}$, $p = -0.72$), indicating that individuals with a higher than typical baseline TPR most likely also have lower than typical baseline SV and HR. The maximum effect on SV ($E_{\text{max,SV}}$) for a 35-yr-old individual was $-23.5\%$, and the magnitude of $E_{\text{max,SV}}$ was expected to increase by 29.7% for every 10-yr increase in age.

The goodness-of-fit plots showed no trend of model misspecification for the final mechanism-based model (Online Supplementary 6, Figs 6–1,6-2, and 6-3). Similarly, the prediction-corrected visual predictive check plots (Online Supplementary 6, Figs 6–4,6-5, and 6-6) show good in-sample predictive performance. The parameter uncertainty, estimated by the sampling importance resampling procedure, showed acceptable precision. Diagnostic plots of sampling importance resampling are shown in Online Supplementary 7, Figs 7–1.

**Effects of propofol infusion in young and older adults**

Figure 2 shows the steady-state concentration–effect relationship for MAP, HR, and SV for a 35-yr-old individual according to the final mechanism-based model. MAP decreases from 86 mm Hg in the absence of propofol to 54 mm Hg at 10 µg ml$^{-1}$ (relative decrease = $-37.2\%$). HR changes from 56 to 87 beats min$^{-1}$ as plasma concentration increases from 0 to 10 µg ml$^{-1}$ (relative increase = $35.6\%$). SV decreases slightly (from 82.9 to 75.6 ml) at low plasma propofol concentration (0–1.1 µg ml$^{-1}$) and then increases to 91.2 ml as plasma concentration increases to 10 µg ml$^{-1}$.

**Discussion**

We developed a mechanism-based pharmacodynamic model that describes propofol-induced changes in MAP, TPR...
Propofol is known to reduce sympathetic tone and influence smooth muscle Ca$^{2+}$ flux, leading to vasodilation, reduced TPR, and ultimately lower blood pressure.\textsuperscript{6,37,38} Propofol also lowers left ventricular preload, which reduces SV.\textsuperscript{38,39} In line with these findings, we found that propofol reduces the zero-order production rates in the turnover equations for TPR and SV. The steady-state concentration–effect relationship of SV shows a biphasic effect resulting from a propofol-driven reduction in SV at low concentrations ($<1.1$ mg $\cdot$ ml$^{-1}$) and an increase in SV at higher concentrations because of the feedback effect from MAP.

Several studies have demonstrated that propofol reduces the tachycardia response to hypotension because of inhibition of the baroreceptor reflex.\textsuperscript{37,38,40} Despite these observations, we found that HR significantly increased in healthy volunteers receiving propofol. A possible explanation is that the implemented as a latent variable), SV (approximated by PP), and HR, and the interrelationship between these variables in healthy volunteers. According to our model, propofol decreases TPR and SV with a relatively greater sensitivity of TPR (the estimated maximum effects of propofol on TPR and SV were $-85.1\%$ and $-23.5\%$, respectively). The reduced TPR and SV results in a decrease in MAP, which further influences SV, HR, and TPR through three negative feedback loops. Age was a significant covariate on $E_{\text{max}}$SV in the mechanism-based model, where the propofol-induced decrease in SV was greater in older volunteers. Both our mechanism-based model and our empirical models adequately describe the changes in MAP, HR, and PP after propofol infusion. We also showed the potential utility of the model by showing good agreement between simulations and the data on propofol-induced changes in MAP and HR from Fairfield and colleagues.\textsuperscript{33}

Fig 3. Predicted changes in plasma propofol concentration, MAP, HR, and SV during propofol infusion according to the drug label in adults (left panel) and older individuals (right panel). $C_p$, plasma concentration; SV, stroke volume.
baroreflex-induced increase in HR outweighs the inhibitory effect of propofol on the baroreceptor reflex, and our model describes the net result of these conflicting mechanisms. Our simulations of changes in MAP and HR differed from the observations of Maneglia and Cousin. The discrepancy between the model predictions and observations in older individuals is because our model suggests a strong relationship between the model predictions and observations in older individuals is because our model suggests a strong relationship between age and $E_{max_SV}$ (e.g. $E_{max_SV}$ is $-86.2\%$ for an 85-yr-old individual, whereas $E_{max_SV}$ is $-23.5\%$ for a 35-yr-old individual). According to equation (1), the decrease in MAP from baseline is expected to be greater for an individual with a stronger effect on SV, and the increase in HR will be more pronounced owing to the negative feedback mechanism. Nevertheless, the age relationship on $E_{max_SV}$ needs to be confirmed in our future studies.

We identified a time-dependent effect on haemodynamic variables and hypothesise that this reflects a time-dependent adaptation of the feedback mechanisms in the cardiovascular system in response to propofol exposure. Unfortunately, our data did not allow us to implement this time-dependency in a more mechanistic manner. More data, especially more diverse data in terms of the propofol infusion regimen, are likely needed to improve our understanding of the origin of this time dependency.

Wada and colleagues and Upton and colleagues have shown for thiopental and propofol that drug-induced alterations in liver blood flow can impact the pharmacokinetics. When this is the case, a sequential PK–PD modelling approach, as used in this analysis, is not appropriate and a simultaneous PK–PD modelling approach is more useful.

We used the Eleveld propofol PK model to derive the post hoc PK parameters for all subjects before PD modelling. This PK model assumes linear kinetics and does not take into account potential cardiac output or liver blood flow dependent pharmacokinetics. Nevertheless, goodness-of-fit plots (Online Supplementary Figs 3–1) showed that the Eleveld PK model accurately described the current dataset, suggesting that a propofol-induced decrease in liver blood flow is not present in our subjects and is not confounding our results.

This is the first quantitative analysis of the cardiovascular adverse effects of propofol in a mechanism-based PK–PD model in humans. Several studies have characterised the haemodynamic effects of propofol using more empirical models. Jeleazcov and colleagues developed a PK–PD model to characterise the effects of propofol on MAP in which the concentration–effect relationships was described by a direct response model with two effect-site compartments. These two effect sites indicate that the effect of propofol on MAP is mediated by two pathways (e.g. changes in CO and systemic vascular resistance). When we use the model by Jeleazcov and colleagues (ignoring the differences in pharmacokinetic models) to predict the maximum decrease in MAP according to our study design, results are very similar (~38.8% for a 35-yr-old individual in our model vs ~47.9% for the model by Jeleazcov and colleagues).

Wu and colleagues developed a PK–PD model describing the changes in MAP after propofol administration in normal weight and morbidly obese patients (BMI >35 kg m$^{-2}$). Their model contains an effect-compartment model linked to the central compartment of a two-compartment pharmacokinetic model. We cannot directly compare parameters between the model by Wu and colleagues and our final model as there is no drug effect parameter on MAP in our mechanism-based model. However, when we simulate the maximum effect on MAP after propofol infusion according to our study (for a normal weight patient) using only the pharmacodynamic model presented by Wu and colleagues, results are in good agreement. In the model by Wu and colleagues, MAP decreased from 96 to 62 mm Hg (relative decrease of ~35.1%), whereas our model predicts a decline in MAP from 90 to 55 mm Hg (relative decrease of ~38.8%).

Our results are in general agreement with the work of Kazama and colleagues, who developed an effect-site compartmental model for propofol on systolic blood pressure (SBP). The half-lives for dissipation of propofol-induced drug effects on SBP in patients aged 20–39, 40–59, 60–69, or 70–85 yr were 4.68, 5.92, 8.87, and 10.22 min, respectively, which is similar to the estimated value from our mechanistic model (9.19 min). In addition, Kazama and colleagues found that the effect on SBP increased with increasing age. The estimated $EC_{50}$ in these four groups was 4.61, 4.13, 3.96, and 2.09 mg min$^{-1}$, respectively. In our model, a similar effect was found with $E_{max_SV}$ increasing with increasing age, resulting in a decrease in MAP during propofol infusion with increasing age.

The model by Snelder and colleagues was used as a starting point in our mechanism-based model development. There are several differences between the models. First, the Snelder model was developed based on data from rats whereas our study used data from humans. Although there are differences between rats and humans in cardiac electrophysiology, the structure we used for our model is...
physiologically reasonable. Second, the Snelder model was developed using experimental data where SV was measured directly, whereas for our study SV measurements were unavailable and we used PP data as a surrogate of SV. Third, feedback mechanisms were implemented as linear relationships between MAP and the rate constant product of HR, SV, and TPR in Snelder’s model, whereas a power function describes our data better. Finally, circadian rhythm was not included in our model because of the short time course of the study (~5 h). There are also similarities between the two models. The structure of our mechanism-based model is the same as that of the Snelder model and only differs in implementation of the drug effect. Moreover, both models account for a potential time-varying effect that causes a temporary increase in HR and MAP.

The Snelder model was further extended by Venkatasubramanian and colleagues on data in dogs to include cardiac contractility (dP/dt\text{max}). In this refined model, a more detailed mechanistic description of SV was used that included cardiac contractility and HR. Despite this refinement, translation from dP/dt\text{max} to any clinical measure of contractility is still under debate and warrants further investigation.

Chae and colleagues used a similar mechanistic model to describe the haemodynamic changes induced by telmisartan in healthy male volunteers. Their model also includes the interrelationships between haemodynamic variables and baroreflex feedback control. There are still several differences between our mechanism-based model and the model developed by Chae and colleagues. Baroreflex control is described in the Chae model by a turnover function taking into account the fractional change in MAP, whereas we estimated the parameter FB representing the power of feedback similar to the Snelder model. In our dataset, the approach by Chae and colleagues performed worse than using the parameter FB as in our final model. In addition, the inverse relationship between HR and SV is not included in the Chae model.

Bahnsawy and colleagues modified the Chae model by including the inverse relationship between HR and SV. To describe the short-term changes in haemodynamics, \( k\text{out} \) was fixed to 35 h\(^{-1}\) (half-life of 1.20 min), which is in the same order magnitude as estimates from our model (9.19 min). Bahnsawy and colleagues also showed that baseline SV needs to be fixed if there are only MAP and HR measurements to keep the model identifiable, whereas in our model PP was included, which served as a surrogate of SV and therefore baseline SV could be estimated.

Application of a mechanism-based PK–PD model allows a more granular description to complex physiological systems, leading to better understanding of the system through separation of drug-specific parameters (e.g. \( E\text{max} \) and EC\(_{50}\)) and biological system-specific parameters (e.g. \( k\text{out} \) and FB). This property enables better understanding of changes amongst the haemodynamic effects by simultaneously considering both drug effect and correlations between cardiovascular effects.

There are some limitations to our study. First, we used data from healthy volunteers. Although noxious stimuli were applied, we acknowledge that the level of noxious stimulation was less than that during surgery. However, use of healthy volunteer data is a strength in that it allows us to calibrate the model to data that lack confounding factors that are known to be present in patient data (medications, cardiovascular disease, etc.). It is reassuring that predictions from our final model are in reasonable agreement with results from studies in patients. In a follow-up project, this model will serve as a basis to describe the haemodynamic effects of propofol–remifentanil combinations both in healthy volunteers and in patients, which will explore additional factors that can help explain the variability that we observe in the drug-induced haemodynamic responses.

Second, we did not have SV measurements and so used PP as a surrogate of SV based on the assumption that total arterial compliance remained constant. Nevertheless, propofol can cause an increase in compliance. At the same time, the ratio of SV to PP has been shown to be related to body size, age, and heart rate. A sensitivity analysis showed that our data are not informative for estimating SV/PP ratio or for applying a more mechanistic equation such as the equation presented by de Simone and colleagues. As a consequence, predicted changes in SV or CO from our model remain uncertain and should be evaluated in future research.

In conclusion, we present a mechanism-based pharmacodynamic model for propofol effects on MAP, HR, SV, and TPR in healthy volunteers. The mechanism-based model performance is equally good to the performance of three empirical models for MAP, HR, and PP. The similarities between model simulations and published observations indicate that the model has reasonable predictive properties.

Authors’ contributions
Study design: MMRFS, PC
Data analysis: HS, DJE, PC
First draft of the paper: HS
Revision of the manuscript: DJE, MMRFS, PC

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Declarations of interest
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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.01.022.

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