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Pharmacodynamic mechanism-based interaction model for the haemodynamic effects of remifentanil and propofol in healthy volunteers

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Abstract

Background: Propofol and remifentanil are frequently combined for the induction and maintenance of general anaesthesia. Both propofol and remifentanil cause vasodilation and potentially reduce arterial BP. We aimed to develop a mechanism-based model that characterises the haemodynamic interactions between remifentanil and propofol.
Methods: Data from two clinical trials in healthy volunteers were analysed using remifentanil-alone, propofol-alone, and combination groups. We evaluated remifentanil effects on haemodynamics using a previously developed mechanism-based haemodynamic model of propofol. The interaction between propofol and remifentanil was explored using the principles of the general pharmacodynamic interaction (GPDI) model.
Results: Remifentanil alone increased the dissipation rate of total peripheral resistance by 50% at 3.0 ng ml^{-1}. Additionally, the dissipation rates of HR and stroke volume were attenuated by 4.8% and 4.9% per 1 ng ml^{-1} increase in remifentanil concentration, respectively. The maximal effect of propofol alone in decreasing the production rate of total peripheral resistance was 78%, which decreased to 32% when combined with remifentanil 4 ng ml^{-1}. The effects of remifentanil on HR and stroke volume were attenuated by propofol with maximum decreases of 11.9% and 21.2%, respectively. Goodness-of-fit plots and prediction-corrected visual predictive check plots showed good predictive performance of the models.
Conclusions: The structure of the previous mechanism-based haemodynamic model for propofol was able to describe the effects of remifentanil alone on haemodynamic variables. The GPDI model provided a good framework for characterising the pharmacodynamic interaction between remifentanil and propofol on haemodynamic properties.
Clinical trial registration: NCT02043938; NCT03143972.

Keywords: haemodynamic; healthy volunteers; interaction; mechanism-based pharmacodynamic modelling; propofol; remifentanil

Editor's key points

- Remifentanil and propofol are frequently combined during general anaesthesia in clinical practice, but few empirical models have investigated the interactions between remifentanil and propofol on cardiovascular function.
- A general pharmacodynamic interaction model identified an antagonistic interaction on heart rate, a synergistic interaction on stroke volume, and a mixed synergistic–antagonistic interaction on mean arterial pressure between remifentanil and propofol.
- This study extends a previously described mechanism-based haemodynamic model for propofol to quantify the haemodynamic effects of remifentanil and their interactions to facilitate prediction of the haemodynamic effects of general anaesthesia.

Remifentanil is a short-acting μ-opioid agonist with analgesic properties,[1] and propofol is an allosteric agonist of the Type A γ-aminobutyric acid receptor that is a fast-acting hypnotic drug.[2] The combination of these drugs is frequently used for induction and maintenance of sedation and general anaesthesia in clinical practice. However, both remifentanil and propofol have dose-dependent haemodynamic side-effects.[2–4] Hypotension induced by general anaesthesia is associated with increased postoperative morbidity and mortality.[5] Understanding the relationship between exposure to anaesthetic drugs and haemodynamic variables could contribute to preventing haemodynamic side-effects, such as hypotension, in clinical practice.

The haemodynamic side-effects of remifentanil are caused by vagal activation, which results in reduced MAP, cardiac output, and systemic vascular resistance.[1,3] The haemodynamic side-effects of propofol are the results of a decrease in sympathetic tone, which reduces total peripheral resistance (TPR) and thereby lowers MAP.[2] Propofol also lowers stroke volume (SV) by decreasing the preload of the left ventricle.[6,7]

The haemodynamic effects of propofol have been described previously in a mechanism-based haemodynamic model in healthy volunteers.[7] The haemodynamic effects of remifentanil on MAP have only been described empirically without consideration of feedback mechanisms between TPR, SV, HR, and MAP.[8] The interaction between remifentanil and propofol on MAP and HR separately has been quantified using response surface models.[9] However, response surface models have limitations because they draw inference on the types of interactions between two drugs (infra-additive, additive, or synergistic) at the effect level only, by comparing a predicted additive response based on the single-drug effect using an additivity model (e.g. Loewe additivity or Bliss independence) with the observed response. Although useful for qualifying drug interactions, response surface models are less useful for simulation, as they do not quantify the interaction at the parameter level. In contrast, mechanism-based models with drug effects incorporated using the general pharmacodynamic interaction (GPDI) model do not have these limitations. The two primary aims of this study were therefore (i) to extend the previously developed mechanism-based haemodynamic model of propofol to characterise the effect of remifentanil alone on haemodynamic variables in healthy volunteers, and (ii) to describe the interaction between remifentanil and propofol on haemodynamic variables quantitatively using the GPDI model.

Methods

Study design

Data from two clinical trials[10,11] in healthy volunteers without surgical stimuli were re-analysed in this study. Data for the remifentanil-alone group were obtained from the trial by Weerink and colleagues,[10] which was approved by the Foundation for the Evaluation of Ethics in Biomedical Research, Assen, the Netherlands (Medical Research Ethics Committee approval number NL61190.056.17) and registered at ClinicalTrials.gov (NCT03143972). A total of 30 volunteers received a target-controlled infusion (TCI) of remifentanil in a step-up manner at effect-site target concentrations of 1, 2, 3, 5, and 7 ng ml^{-1} using the Eleveld pharmacokinetic model,[12] followed by a 30 min washout. Each target was maintained for 12 min to reach equilibrium, and blood samples were taken at the end of the equilibration time.[10] The trial by Kuizenga and colleagues[11] was approved by the Institutional Review Board of the University Medical Center Groningen (NL43238.042.13) and registered at ClinicalTrials.gov (NCT02043938), and it included healthy volunteers stratified by age and sex. Volunteers received drug infusions on two separate days. On the first day, each volunteer received propofol using TCI in a step-up and step-down titration scheme targeting effect-site concentrations of 0.5, 1, 1.5, 2.5, 3.5, 4.5, 6, and 7.5 μg ml^{-1} followed by a single bolus using the Schnider pharmacokinetic–pharmacodynamic model (the propofol-alone group).[13,14] On the second day (>1 week after the first study day), volunteers were randomised across two (2 or 4 ng ml^{-1}) remifentanil groups, and they were again dosed according to the same step-up and step-down scheme for propofol. Remifentanil was administered *via* TCI using the Minto pharmacokinetic–pharmacodynamic model (the combination group).[15,16]

Haemodynamic measurements and data handling

In the trial by Weerink and colleagues,[10] systolic BP, diastolic BP, and MAP were measured using a radial artery catheter (IntelliVue MP70® monitor; Philips, Amsterdam, the Netherlands). HR was derived from standard three-lead ECG. All variables were collected every 15 s using RugloopII software (Demed, Temse, Belgium). In the trial by Kuizenga and colleagues,[11] ECG and noninvasive BP measurements were obtained from a Philips IntelliVue MP50 vital signs monitor (Philips Medizin Systeme, Böblingen, Germany). Noninvasive MAP, systolic BP, and diastolic BP were measured every minute. HR was derived from the ECG and was recorded every second. All variables were collected using RugloopII software. Pulse pressure (PP) was calculated from the measured systolic and diastolic BP in both studies.

For the remifentanil-alone group, invasive haemodynamic measurements were influenced by the collection of blood samples. To account for this influence, we removed HR and BP measurements 2 min before and after the time of blood sample collection. We applied a median filter to reduce the influence of artifacts in the data or outlying observations for the remifentanil-alone and combination groups, as described.[7]

Population pharmacokinetic–pharmacodynamic modelling

Pharmacokinetics of remifentanil and propofol

The pharmacokinetics of remifentanil and propofol were characterised using the individual pharmacokinetic parameter approach.[17] Individual *post hoc* pharmacokinetic parameters (CL, Q2, Q3, V1, V2, and V3) for remifentanil and propofol were derived from the Eleveld pharmacokinetic models for remifentanil[12] and propofol.[18]

Mechanism-based haemodynamic model of remifentanil

Data from the remifentanil-alone group were used to develop a mechanism-based haemodynamic model for remifentanil. The structural model was based on the previously described mechanism-based haemodynamic model for propofol.[7] In the structural model, PP was used as a surrogate of SV (SV/PP=1.5).[7] Remifentanil drug effects were explored on turnover equations of TPR, SV, and HR using linear, log-linear, E_{max}, and sigmoid E_{max} models. The remifentanil drug effects were implemented on zero-order production rate constants (k_{in}) or first-order dissipation rate constants (k_{out}) of the turnover equations. Time-dependent effects were further explored to describe elevated MAP, HR, and PP before the start of the remifentanil infusion. Correlations between covariates and *post hoc* predicted parameters, for which between-subject variability (BSV) was included, were graphically explored. The potential influence of covariate effects was formally evaluated by comparing the change in objective function value (OFV) between competing models. The criteria for inclusion of covariates were a decrease in OFV of >3.84 points. Age, weight, height, sex, and BMI were considered as potential covariates.

Mechanism-based haemodynamic model for combined remifentanil and propofol infusions

On top of the time-dependent effects on HR, we explored time-dependent effects on TPR and SV for the mechanism-based haemodynamic model for propofol. The mechanism-based haemodynamic model for the combination of remifentanil and propofol (further referred to as the interaction model) was investigated using the GPDI model.[19] Data from the remifentanil-alone, propofol-alone, and combination groups were simultaneously fitted to develop the interaction model.

In the GPDI model, the effects of remifentanil (E_{max} or linear model) on haemodynamics can be altered concentration-dependently by propofol and vice versa. Example model structures are displayed in the box, where remifentanil and propofol can interact with each other on E_{max} [equations (1) and (2)] or EC_{50} [equations (3) and (4)] if the drug effect is implemented by the E_{max} model, or on the slope for linear effect [equation (5)] Box 1.

In these equations, E_{PROP} and E_{REMI} represent the effects of propofol and remifentanil, respectively; E_{max_PROP} and E_{max_REMI} are the maximum effects of propofol and remifentanil, respectively; EC_{50PROP} and EC_{50REMI} represent the propofol and remifentanil concentrations that produce 50% of the maximum drug effects, respectively; C_{P_RPOP} and C_{P_REMI} represent the plasma concentrations of propofol and remifentanil, respectively; $\gamma_{\_PROP}$ and $\gamma_{\_REMI}$ represent the Hill coefficients for propofol and remifentanil, respectively; SL_{REMI} is the slope of the linear effects of remifentanil; and INT_{PR}

Box 1

Equations for an example GPDI model.

$$E_{PROP} = \frac{E_{max\_PROP} \times \left(1 + \frac{INT_{PR} \times C_{P\_REMI}}{EC50INT_{PR} + C_{P\_REMI}}\right) \times C_{P\_PROP}^{\gamma-PROP}}{EC50_{PROP}^{\gamma\_PROP} + C_{P\_PROP}^{\gamma\_PROP}} \quad (1)$$

$$E_{REMI} = \frac{E_{max\_REMI} \times \left(1 + \frac{INT_{RP} \times C_{P\_PROP}}{EC50INT_{RP} + C_{P\_PROP}}\right) \times C_{P\_REMI}^{\gamma-REMI}}{EC50_{REMI}^{\gamma-REMI} + C_{P\_REMI}^{\gamma\_REMI}} \quad (2)$$

$$E_{PROP} = \frac{E_{max\_PROP} \times C_{P\_PROP}^{\gamma-PROP}}{EC50_{PROP}^{\gamma-PROP} \times \left(1 + \frac{INT_{PR} \times C_{P\_REMI}}{EC50INT\_PR + C_{P\_REMI}}\right) + C_{P\_PROP}^{\gamma-PROP}} \quad (3)$$

$$E_{REMI} = \frac{E_{max\_REMI} \times C_{P\_REMI}^{\gamma-REMI}}{EC50_{REMI}^{\gamma-REMI} \times \left(1 + \frac{INT_{RP} \times C_{P\_PROP}}{EC50INT_{RP} + C_{P\_PROP}}\right) + C_{P\_REMI}^{\gamma-REMI}} \quad (4)$$

$$EFF_{REMI} = \left(SL_{REMI} + \frac{INT_{RP} \times C_{P\_PROP}}{EC50_{PROP} + C_{P\_PROP}}\right) \times C_{P\_REMI} \quad (5)$$

represents the magnitude of the maximum change in E_{max} of propofol caused by remifentanil and vice versa for INT_{RP}.

When the interaction terms are implemented for E_{max} (equations 1 and 2), interpretations of the INT parameters are as follows: $INT_{PR}=0$ indicates no interaction; $INT_{PR} >0$ indicates an increase in E_{max}, representing synergy; and $INT_{PR} <0$ indicates a decrease in E_{max}, representing antagonism. When the interaction terms are implemented for EC_{50} [equations (3) and (4)], interpretation of the INT parameters are as follows: $INT_{PR}=0$ indicates no interaction; $INT_{PR} >0$ indicates an increase in EC_{50}, representing antagonism; and $-1< INT_{PR} <0$ indicates a decrease in C_{50}, representing synergy.

As a starting point for development of the interaction model, we considered a model without interactions (the combination-null interaction model, INT=0). Refinements to this model, in line with the structure of the GPDI model, were explored in a sequential approach (i.e. adding one interaction term at a time). The criteria for inclusion of an interaction effect in the model were a decrease in OFV of >3.84 points, improvement in the prediction-corrected visual predictive checks, and standard goodness-of-fit plots. We also applied backward elimination on the final model and excluded interaction terms if OFV increased <6.64 points (the 1% significance level critical quantile of the corresponding χ^2 distribution) upon removal of a specific interaction component.

Parameter estimation and model evaluation

Data were fitted using the first-order conditional estimation method with interaction using NONMEM (version 7.5; Icon Development Solutions, Hannover, MD, USA). ADVAN13 and tolerance 12 subroutines were applied in the estimation. BSV was described using exponential or additive models. Residual variability was estimated using additive or proportional error models. Goodness of fit was graphically evaluated by plotting the individual or population predictions *vs* the observations and the conditionally weighted residuals *vs* population predictions and time. Parameter uncertainty of the models was estimated using the covariance step in NONMEM or sampling importance resampling.[20] Prediction-corrected visual predictive checks were used to evaluate models internally.[21] All models and simulations were run using PsN (version 5.2.6)[22] and Pirana (version 3.0.0)[23] as back end and front end to NONMEM. Graphical assessment of goodness of fit and

simulations and construction of prediction-corrected visual predictive checks were conducted in R (R Foundation for Statistical Computing, Vienna, Austria).[24]

Simulations of the interaction model

The final interaction model was used to simulate the concentration−effect relationship for MAP, HR, and SV for a 35-yr-old individual receiving propofol or propofol plus remifentanil 2 or 4 ng ml^{-1}. Similar simulations were produced for the combination-null interaction model to evaluate the clinical relevance of the differences in predictions between the combination-null interaction model (INT=0) and the final interaction model.

Finally, we performed 1000 simulations to predict the expected changes in haemodynamics when remifentanil and propofol are administered simultaneously according to the dosing recommendations described in the propofol[25] and remifentanil[26] US Food and Drug Administration (FDA)-approved drug labelling. According to the label, adults (<55 yr of age) should receive propofol at an induction dose of 1.5 mg kg^{-1} over 60 s, followed by a maintenance dose of 0.1 mg kg^{-1} min^{-1}, along with a continuous infusion of remifentanil at 0.1 μg kg^{-1} min^{-1}. We simulated the haemodynamic effects for three people (aged 22, 47, and 60 yr), which represent the median age of the three age groups in the pooled study dataset. These typical individuals were assumed to be males weighing 70 kg with a height of 180 cm.

Results

The patient characteristics of the healthy volunteers are summarised in Supplementary Tables 2−1 In summary, 30 and 36 individuals stratified by age and sex were included in the remifentanil-alone and propofol-alone groups. Individuals in the propofol-alone group were then randomly separated into two combination groups (propofol combined with remifentanil 2 or 4 ng ml^{-1}). The measured plasma concentrations of remifentanil and propofol and the observed MAP, HR, and PP for both the remifentanil-alone and combination groups are shown in Supplementary Figs. 2−1, 2-2, and 2-3.

No bias for either the Eleveld remifentanil and Eleveld propofol pharmacokinetic models (Supplementary Figs. 1−1, 1-2, and 1-3) was observed in the pharmacokinetic prediction for simultaneous administration of both drugs.

For the remifentanil-alone group, the median MAP decreased from 90 mm Hg [95% quantile: 72−112 mm Hg] at baseline to 77 mm Hg [95% quantile: 57−96 mm Hg] at the target concentration of 2 ng ml^{-1}, and then it increased to 82 mm Hg [95% quantile: 64−102 mm Hg] at the target concentration of 7 ng ml^{-1}. Similarly, PP decreased from 74 mm Hg [95% quantile: 45−93 mm Hg] to 61 mm Hg [95% quantile: 36−78 mm Hg] at 2 ng ml^{-1}, and then it increased to 64 mm Hg [95% quantile: 38−110 mm Hg] at the target concentration of 7 ng ml^{-1}. HR decreased from 60 beats min^{-1} [95% quantile: 48−85 beats min^{-1}] at baseline to 57 beats min^{-1} [95% quantile: 46−75 beats min^{-1}] at the target concentration of 2 ng ml^{-1}, and it increased to 66 beats min^{-1} [95% quantile: 44−100 beats min^{-1}] at the target concentration of 7 ng ml^{-1}.

For the combination group, the median MAPs were 55 mm Hg [95% quantile: 52−81 mm Hg] and 51 mm Hg [95% quantile: 43−59 mm Hg] when propofol was combined with remifentanil 2 and 4 ng ml^{-1}, respectively, at a propofol target concentration of 7.5 μg ml^{-1}. When combined with remifentanil 2 ng ml^{-1}, the median HR changed slightly (varied within 59−67 beats min^{-1}), and when combined with remifentanil 4 ng ml^{-1}, it remained stable (varied within 62−69 beats min^{-1}) at low propofol concentrations and increased at a propofol target concentration of 7.5 μg ml^{-1} (median HR: 84 beats min^{-1} [95% quantile: 68−108 beats min^{-1}]). Changes in MAP, HR, and PP for propofol alone and the combination at different propofol target concentrations are summarised in Table 1.

Development of the interaction model

Development of the mechanism-based haemodynamic model of remifentanil is described in Supplementary material 3. In brief, the structure of the mechanism-based haemodynamic model for remifentanil is the same as the previously described mechanism-based model for propofol.[7] Remifentanil effects were implemented on k_{out} for TPR (sigmoid E_{max} model), HR (linear model), and SV (linear model). Time-dependent effects were addressed on HR and SV. We also explored an additional time-dependent effect on SV in our mechanism-based haemodynamic model of propofol,[7] and OFV decreased by −271.1.

For development of the interaction model, the mechanism-based model was defined as the combination-null interaction model, and the deviation from this mechanism-based model prediction from the single-drug data was characterised by the GPDI model. Inclusion of an interaction term (propofol influences remifentanil) for the effect of remifentanil on HR significantly improved model fit (ΔOFV=−224.5) compared with the combination-null interaction model. The model was further expanded by inclusion of interaction terms for drug effects on TPR (propofol influences remifentanil, ΔOFV=−297.7, and remifentanil influences propofol, ΔOFV=−175.7). Finally, an interaction term for the effect of remifentanil on SV (propofol influences remifentanil, ΔOFV=−1132.2) was included. During backward elimination, OFV decreased by 23.3 points when excluding the interaction term for TPR (propofol affecting remifentanil), so this effect was removed from the model. We further modified the model by fixing the Hill coefficient of remifentanil on the effect on TPR to 1 because of instability in the parameter estimation, despite an OFV increase by 60.6 points. Prediction-corrected visual predictive checks and goodness-of-fit plots were not different after fixing these model parameters.

Final interaction model

The final interaction model is shown in equations (6)−(17) (Boxes 2 and 3), with the structure of the model shown in Fig. 1 and the code of the final interaction model presented in Supplementary material 6. Parameter estimates and associated relative standard errors for the interaction model are shown in Table 2.

The variables 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. 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 the power term of the negative feedback of MAP on TPR, SV, and HR. HR_SV is a constant that represents the magnitude of the direct inverse effect of HR on SV. $E_{max\_PROP\_TPR}$, $E_{max\_PROP\_SV}$, and $E_{max\_REMI\_TPR}$ are the maximal effects of propofol on TPR, SV, and remifentanil on TPR, respectively. EC$_{50PROP\_TPR}$,

Table 1 Observed median and 95% quantile for MAP, HR, and pulse pressure (PP) at different propofol effect-site target concentrations for propofol alone and combined with two remifentanil effect-site concentrations.

Propofol target concentration (μg ml⁻¹)	Variable	0	0.5	1	1.5	2.5	3.5	4.5	6	7.5
Propofol alone	MAP (mm Hg)	81 [59−108]	86 [65−104]	80 [64−100]	73 [57−99]	70 [53−100]	65 [49−95]	63 [47−91]	57 [45−80]	55 [44−75]
	HR (beats min⁻¹)	63 [41−83]	61 [37−77]	62 [41−81]	65 [42−87]	67 [49−93]	72 [54−102]	74 [55−105]	76 [55−104]	86 [67−105]
	PP (mm Hg)	50 [29−78]	44 [24−70]	47 [27−69]	47 [27−70]	50 [28−73]	51 [28−73]	53 [28−73]	58 [29−73]	61 [44−76]
Propofol plus remifentanil 2 ng ml⁻¹	MAP (mm Hg)	79 [55−113]	76 [57−98]	68 [54−100]	65 [49−98]	58 [45−94]	55 [44−84]	56 [47−73]	57 [49−80]	55 [52−81]
	HR (beats min⁻¹)	65 [46−86]	59 [43−80]	59 [44−72]	59 [46−89]	62 [48−81]	63 [57−80]	65 [58−74]	67 [60−73]	67 [63−72]
	PP (mm Hg)	51 [30−81]	53 [32−82]	50 [31−77]	49 [31−73]	49 [31−70]	48 [31−68]	49 [28−71]	50 [39−75]	52 [42−73]
Propofol plus remifentanil 4 ng ml⁻¹	MAP (mm Hg)	81 [51−113]	81 [59−116]	69 [51−114]	62 [45−100]	59 [43−82]	60 [41−77]	62 [43−78]	57 [43−79]	51 [43−59]
	HR (beats min⁻¹)	69 [45−103]	62 [42−95]	63 [42−95]	62 [42−88]	62 [45−88]	65 [49−91]	67 [51−101]	80 [52−108]	84 [68−108]
	PP (mm Hg)	52 [33−84]	52 [30−85]	49 [30−79]	48 [28−77]	50 [24−74]	50 [26−71]	51 [32−70]	54 [38−72]	55 [40−69]

EC_{50PROP_SV}, and EC_{50REMI_TPR} are the concentrations that produce 50% of the maximal effect of propofol on TPR, SV, and remifentanil on TPR, respectively. INT_{TPR} is the maximum magnitude change of E_{max} of propofol on TPR caused by remifentanil. SL_{REMI_SV} and SL_{REMI_HR} are the slopes of the linear effects of remifentanil on SV and HR, respectively. INT_{SV} and INT_{HR} represent the maximum magnitude changes of slope of remifentanil on SV and HR caused by propofol, respectively. EC_{50INT_HR} is the interaction potency of propofol on the effect of remifentanil on HR.

The effects of remifentanil and propofol on TPR, HR, and SV and the interaction between remifentanil and propofol are shown in equations (12)−(16) (Box 3). In line with the mechanism-based haemodynamic model for propofol,[7] the effect of age on the E_{max} of SV of propofol was confirmed in the interaction model (ΔOFV=−1737), indicating $E_{max\_PROP\_SV}$ increases with increasing age [equation (17)].[7] In equation (17), $E_{max\_PROP\_SV\,(typ)}$ is the population typical value of the maximal effect of propofol on SV:

The final estimations of baseline MAP, HR, and SV were 75 mm Hg, 56 beats min⁻¹, and 83 ml, respectively. The apparent MAP [taking into account the time-dependent effect described in equations (8) and (9)] was 92 mm Hg, which resulted from an increase in HR by 7 beats min⁻¹ and an increase in SV by 7.4 ml before drug administration. The estimated drug effect parameters for the interaction model are comparable with the single models (mechanism-based haemodynamic model for remifentanil and propofol). For instance, the estimated E_{max} for the reduced production rate of TPR (77.8% for the interaction model *vs* 86.0% for the propofol model) of propofol are similar in the single models and interaction model.

According to our final model, HR and SV increased by 3.3% and 5.8% from baseline per 1 ng ml⁻¹ increase in remifentanil concentration (remifentanil alone). The positive effect of remifentanil on HR and SV was attenuated by propofol. (INT_{HR} and INT_{SV} are negative.) This negative interaction was also reflected in Figs. 2 and 3, for remifentanil combined with propofol, when the elevated HR was reduced (purple line *vs* blue line). For SV, the increased SV was reversed when propofol was combined with remifentanil. For TPR, the maximal effect of propofol in decreasing the production rate of TPR was 77.8% when combined with remifentanil 2 or 4 ng ml⁻¹, and the maximal effects of propofol on TPR were reduced to 47.5% and 31.2% (calculated from $E_{max\_PROP\_TPR}$ and INT_{TPR}, respectively).

The goodness-of-fit plots (Supplementary Figs 4−1 to 4-12) and prediction-corrected visual predictive check plots (Supplementary Figs 4−13 to 4-24) showed the model could adequately describe our data with good predictive performance. The diagnostic plots of sampling importance resampling are shown in Supplementary Fig. 4−25.

Effects of remifentanil and propofol combined on haemodynamics

Figs. 2 and 3 show the steady-state plasma concentration−effect relationship (change from baseline) of MAP (left), HR (middle), and SV (right) in a 35-yr-old individual for propofol alone predicted by the mechanism-based haemodynamic model for propofol (purple), propofol combined with remifentanil 2 or 4 ng ml⁻¹ predicted by the combination-null interaction model (green), and the combination interaction

Box 2

Equations of the final interaction model.

$$\frac{dTPR}{dt} = k_{in\_TPR} \bullet RMAP^{FB} \bullet (1 + EFF_{PROP_{TPR}}) - k_{out} \bullet TPR \bullet (1 - EFF_{REMI_{TPR}}) \tag{6}$$

$$\frac{dSV^*}{dt} = k_{in\_SV} \bullet RMAP^{FB} \bullet (1 + EFF_{PROP_{SV}}) - k_{out} \bullet SV^* \bullet (1 - EFF_{REMI_{SV}}) \tag{7}$$

$$\frac{dHR^*}{dt} = k_{in\_HR} \bullet RMAP^{FB} - k_{out} \bullet HR^* \bullet (1 - EFF_{REMI_{HR}}) \tag{8}$$

$$SV = (SV^* + TDE_{SV}) \bullet \left[1 - HR_{SV} \bullet LN\left(\frac{HR}{Base_{HR}}\right)\right] \tag{9}$$

$$HR = HR^* + TDE_{HR} \tag{10}$$

$$RMAP = \frac{HR \bullet SV \bullet TPR}{Base_{HR} \bullet Base_{SV} \bullet Base_{TPR}} \tag{11}$$

Box 3

Equations of the effects of remifentanil and propofol on total peripheral resistance, heart rate and stroke volume.

$$EFF_{PROP_{TPR}} = \frac{\left(E_{max\_PROP\_TPR} + \frac{INT_{TPR} \times C_{P\_REMI}}{EC_{50REMI} + C_{P\_REMI}}\right) \times C_{P\_PROP}^{\gamma\_PROP}}{EC_{50P\_PROP}^{\gamma\_PROP} + C_{P\_PROP}^{\gamma\_PROP}} \tag{12}$$

$$EFF_{REMI_{SV}} = \left(SL_{REMI\_SV} + \frac{INT_{SV} \times C_{P\_PROP}}{EC_{50SV\_PROP} + C_{PROP}}\right) \times C_{P\_REMI} \tag{13}$$

$$EFF_{REMI_{HR}} = \left(SL_{REMI\_HR} + \frac{INT_{HR} \times C_{P\_PROP}}{EC_{50INT\_HR} + C_{PROP}}\right) \times C_{P\_REMI} \tag{14}$$

$$EFF_{PROP_{SV}} = \frac{E_{max\_PROP_{SV}} \times C_{P\_PROP}}{C_{50PROP\_SV} + C_{P\_PORP}} \tag{15}$$

$$EFF_{REMI_{TPR}} = \frac{E_{max\_REMI\_TPR} \times C_{P\_REMI}}{EC_{50REMI\_TPR}^{\gamma\_REMI} + C_{P\_REMI}} \tag{16}$$

$$E_{max\_PROP\_SV} = E_{max\_PROP\_SV(typ)} \bullet e^{(0.033 \bullet (age - 35))} \tag{17}$$

model (blue). When combined with remifentanil 2 ng ml^{-1}, the effect on MAP of propofol combined with remifentanil is greater than the effect of propofol alone at low propofol concentrations (<7.5 μg ml^{-1}). When combined with remifentanil 4 ng ml^{-1}, the effect on MAP for propofol combined with remifentanil is greater than the effect of propofol alone across the propofol concentration range. The deviation of effect on MAP between propofol alone and propofol combined with remifentanil was maximal at a propofol concentration of 1.1 μg ml^{-1}, where MAP decreased by 5.7 %, 14.6%, and 21.5% for propofol alone and propofol combined with remifentanil 2 or 4 ng ml^{-1}, respectively. HR increased by 52.3%, 12.3%, and 1.9% from baseline for propofol alone and propofol combined with remifentanil 2 and 4 ng ml^{-1}, respectively.
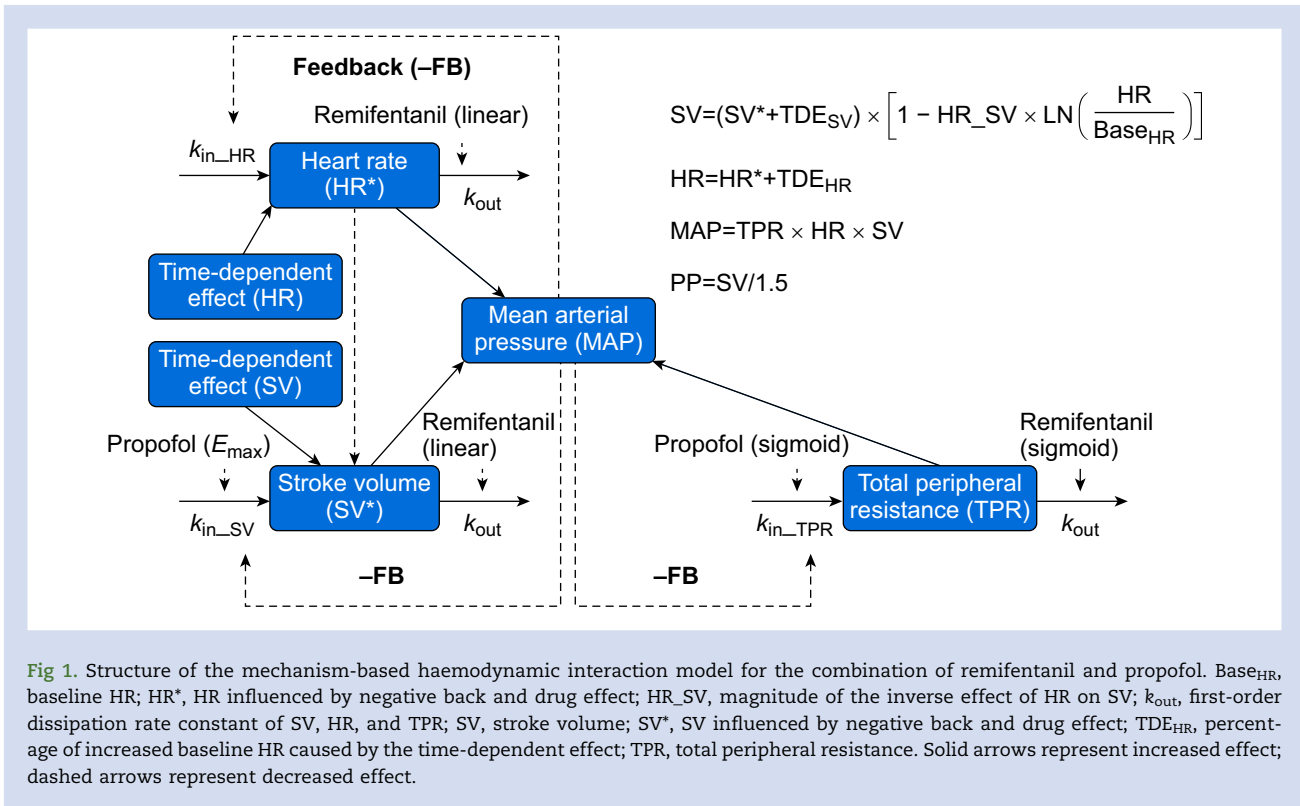
There is an antagonistic interaction between remifentanil and propofol on HR, which can be seen by comparing blue (combination interaction model) and green (combination-null interaction model) lines. For example, when propofol was combined with remifentanil 4 ng ml^{-1}, the predicted changes in HR were 12.3% and 24.3% for the interaction model and combination-null interaction model. The predicted decrease in SV for the combination interaction model (32.5%) is stronger than the combination-null interaction model (7.2%) when propofol was combined with remifentanil 4 ng ml^{-1}, which indicates a synergistic interaction. For MAP, when propofol is combined with remifentanil 2 ng ml^{-1} at low propofol concentrations, the effect simulated by the combination interaction model is greater than the combination-null interaction model, whereas at high propofol concentrations, the effect of

the combination interaction model is lower than the combination-null interaction model. There is a synergistic interaction on MAP when propofol is combined with remifentanil 4 ng ml^{-1}.

Fig. 4 shows the changes in propofol plasma concentration; remifentanil plasma concentration; and relative changes in MAP, HR, and SV from baseline after propofol combined with remifentanil according to the FDA drug label for three individuals of different ages.[25,26] The maximal effect on MAP and SV increased with increasing age (median MAP decreased 32.2% [95% prediction interval: 25.5–37.2%], 36.1% [95% prediction interval: 29.1–41.3%], and 39.6% [95% prediction interval: 32.6–44.9%]) from baseline for individuals aged 22, 47, and 66 yr, whilst median SV decreased to 14.0% [95% prediction interval: 3.2–21.6%], 23.6% [95% prediction interval: 12.6–30.6%], and 32.3% [95% prediction interval: 22.2–38.7%], respectively. Median HR changed slightly (<10% change from baseline) during dosing according to FDA drug label dosing in the three age groups.

Discussion

The structural model of the previously developed mechanism-based haemodynamic model for propofol[7] was also suitable for quantifying the effects of remifentanil on haemodynamic variables. Remifentanil alone decreased TPR and slightly increased HR and PP by altering the dissipation rates of these haemodynamic variables in a concentration-dependent manner. No pharmacokinetic interaction was observed

$$SV=(SV^*+TDE_{SV}) \times \left[1 - HR\_SV \times LN\left(\frac{HR}{Base_{HR}} \right) \right]$$

$$HR=HR^*+TDE_{HR}$$

$$MAP=TPR \times HR \times SV$$

$$PP=SV/1.5$$

Fig 1. Structure of the mechanism-based haemodynamic interaction model for the combination of remifentanil and propofol. $Base_{HR}$, baseline HR; HR^*, HR influenced by negative back and drug effect; HR_SV, magnitude of the inverse effect of HR on SV; k_{out}, first-order dissipation rate constant of SV, HR, and TPR; SV, stroke volume; SV^*, SV influenced by negative back and drug effect; TDE_{HR}, percentage of increased baseline HR caused by the time-dependent effect; TPR, total peripheral resistance. Solid arrows represent increased effect; dashed arrows represent decreased effect.

between propofol and remifentanil; therefore, quantification of drug—drug interaction focused on haemodynamic variables. The GPDI model was able to describe the drug effects on haemodynamic variables for both single drugs alone and the interaction between remifentanil and propofol. Three interaction effects between remifentanil and propofol were identified using the GPDI model that could not be described using the combination-null interaction model. Propofol reduced the effect of remifentanil on HR and SV, and conversely remifentanil reduced the propofol effect on TPR. Variability between subjects in all haemodynamic variables was adequately described by the model.

The fundamental framework of our mechanistic model was developed based on a model presented by Snelder and colleagues.[27] The pressure—volume loop theory has been used to further update the original model of Snelder and colleagues[27] by integrating contractility with cardiac output, as this provided a more mechanistic basis for application of the model.[28] We were not able to use this updated model because it is difficult to measure contractility in humans. Nevertheless, performance of the developed mechanism-based model was acceptable in terms of model fit and prediction of haemodynamic variables. We confirm that the structural model of the mechanism-based haemodynamic model for propofol[7] was also suitable for quantifying the drug effects of remifentanil on haemodynamic variables.

Remifentanil is known to produce cardiovascular depression *via* vagal—cardiac activation, which is thought to originate from peripheral vasodilation leading to hypotension.[1,3] Some studies have shown that remifentanil can cause bradycardia, possibly because of a decrease in sympathetic tone and an

increase in vagal tone as a result of stronger intraoperative anti-nociceptive properties.[3,29,30] Subjects were dosed with both remifentanil and propofol, and as such, it is not clear whether the observed bradycardia is attributable to remifentanil or the combination of remifentanil and propofol. Some studies report tachycardia after dosing with remifentanil alone, which is in line with our findings, as remifentanil increased HR. This might be attributable to negative feedback of the baroreflex system caused by hypotension.[1,31]

Bouillon and colleagues[32] have shown that co-administration of propofol and remifentanil reduces the central volume of distribution and clearance of remifentanil. Our analysis did not indicate a similar pharmacokinetic interaction between remifentanil and propofol. We therefore do not expect an influence of combined administration of remifentanil and propofol on the pharmacokinetics of the individual drugs. Thus, co-administration of remifentanil and propofol did not influence model performance of the mechanism-based interaction model.

The pharmacodynamic drug—drug interaction between remifentanil and propofol on haemodynamics has been investigated by Nieuwenhuijs and colleagues.[9] They developed models for HR and MAP separately using response surface modelling and found additive interactions between remifentanil and propofol. We applied GPDI model principles to describe the pharmacodynamic drug—drug interaction between remifentanil and propofol, which allows us to predict both single-drug effects and interactions without changing the single-model structures.[19] Using this approach, a non-additive interaction between propofol and remifentanil could be quantified, which differs from the model of

Table 2 Parameter estimates of final interaction model. *Calculated according to $\sqrt{e^{\omega^2}-1}\times 100\%$. $Base_{SV}$, $Base_{HR}$, and $Base_{TPR}$, baseline SV, HR, and TPR; BSV, between-subject variability; EC_{50TPR}, concentrations that produce half of the maximal remifentanil effect of TPR; E_{max_TPR}, maximum effect of remifentanil on TPR; FB, magnitude of the feedback; FIX, parameter values kept unchanged during estimation; HR_SV, magnitude of the inverse effect of HR on SV; k, first-order dissipation rate constant of the time-dependent effect; k_{out}, first-order dissipation rate constant for SV, HR, and TPR; $LTDE_{SV}$ and $LTDE_{HR}$, percentage of increased baseline SV and HR caused by the time-dependent effect; PP, pulse pressure; RSE, relative standard error; SL_{HR} and SL_{SV}, slope of remifentanil effect on HR and SV; SV, stroke volume; TPR, total peripheral resistance; γ, Hill coefficient for TPR sigmoid; ρ, correlation coefficient; σRUV, residual unexplained variability.

Parameter	Estimate (RSE %)	95% Confidence interval	
		Lower	Upper
k_{out} (min^{-1})	0.072 (2.8)	0.068	0.076
$Base_{SV}$ (ml)	82.2 (0.7)	81.3	83.3
$Base_{HR}$ (beats min^{-1})	56 (0.9)	55	57
$Base_{TPR}$ (mm Hg ml^{-1} min^{-1})	0.016 (2.4)	0.016	0.017
FB	0.66 (1.7)	0.64	0.68
HR_SV	0.312 FIX		
k (min^{-1})	0.067 (4.3)	0.061	0.072
$LTDE_{SV}$ (%)	0.090 (4.7)	0.082	0.098
$LTDE_{HR}$ (%)	0.12 (5.2)	0.11	0.13
EC_{50PROP_TPR} (μg ml^{-1})	3.21 (2.8)	3.05	3.38
$E_{max\_PROP\_TPR}$ (%)	−0.78 (1.6)	−0.80	−0.75
γ_{PROP}	1.83 (3.9)	1.69	1.97
EC_{50PROP_SV} (μg ml^{-1})	0.44 (2.9)	0.42	0.47
$E_{max\_PROP\_SV}$ (%)	−0.15 (3.5)	−0.16	−0.14
$AGE\_E_{max\_SV}$	0.033 (3.5)	0.031	0.036
EC_{50REMI_TPR} (ng ml^{-1})	4.59 (1.7)	4.44	4.76
$E_{max\_REMI\_TPR}$ (%)	−1 FIX		
SL_{REMI_HR} (ng ml^{-1})	0.033 (5.9)	0.029	0.036
SL_{REMI_SV} (ng ml^{-1})	0.058 (7.0)	0.051	0.066
INT_{HR} (ng ml^{-1})	−0.12 (3.3)	−0.13	−0.11
EC_{50INT_HR} (μg ml^{-1})	0.20 (2.9)	0.19	0.21
INT_{TPR} (%)	100.00 (2.3)	95.87	104.51
INT_{SV} (ng ml^{-1})	−0.21 (3.3)	−0.23	−0.20

Parameter	BSV%* (RSE %)	95% Confidence interval	
		Lower	Upper
BSV_Base_{SV}	18.3 (7.6); $\rho Base_{TPR}$ −0.58 (7.1)	16.98	19.60
BSV_Base_{TPR}	23.3 (4.1); $\rho Base_{HR}$ −0.65 (8.3)	22.47	24.35
BSV_Base_{HR}	15.67 (7.0)	14.68	16.83
$BSV\_C_{50PROP\_TPR}$	74.34 (3.9)	70.50	77.56
$BSV\_E_{max\_REMI\_TPR}$	75.30 (3.3)	72.07	78.26
$BSV\_SL_{REMI\_HR}$	6.18 (12.1); ρSL_{REMI_SV} 0.57 (13.7)	5.40	6.87
$BSV\_SL_{REMI\_SV}$	9.34 (8.9)	8.60	10.20
σRUV_Proportional_MAP (%)	11.04 (1.5)	10.88	11.19
σRUV_Proportional_HR (%)	10.42 (1.5)	10.27	10.57
σRUV_Proportional_PP (%)	17.12 (1.6)	16.88	17.38

Nieuwenhuijs and colleagues,[9] which predicts that MAP will decrease by 10.6% from baseline (at remifentanil 1 ng ml^{-1} and propofol 1 μg ml^{-1}), and HR will decrease by 16.3%. Our model predicts a similar decrease in MAP (11.7%) but a less pronounced effect on HR (2.7%). This discrepancy in predicted HR might partially be explained by the homogenous population in their study, which had a limited range of covariates (healthy males aged 19–25 yr) and prevents reliable evaluation of covariate effects on haemodynamic variables. Furthermore, the dose ranges in their study were relatively low (propofol 0–2.6 μg ml^{-1}; remifentanil 0–2.0 ng ml^{-1}) compared with our study. Another reason could be that the baroreflex feedback mechanism, which accounts for the increased HR caused by hypotension, was not considered in their study. Therefore, the clinical utility of their study might be limited in terms of its ability to describe mechanistically the interaction between remifentanil and propofol on haemodynamics.

We performed a simulation based on the dosing regimen used by Turgut and colleagues[33] to evaluate the potential utility of the interaction model. After induction and maintenance of anaesthesia with propofol and remifentanil, the mean MAP decreased from 95 to 80 mm Hg in their study, which is in line with predictions from our model with a 95% prediction interval for baseline MAP of 73–117 mm Hg and a MAP during maintenance of anaesthesia between 44 and 84 mm Hg. Their observed changes in HR are also within the 95% prediction intervals from our interaction model.

Our simulations are also in general agreement with observations by Meijer and colleagues,[34] who found that 43% of patients experienced a MAP <60 mm Hg, which was 52.5% in our simulations according to their dosing regimen. Similarly,
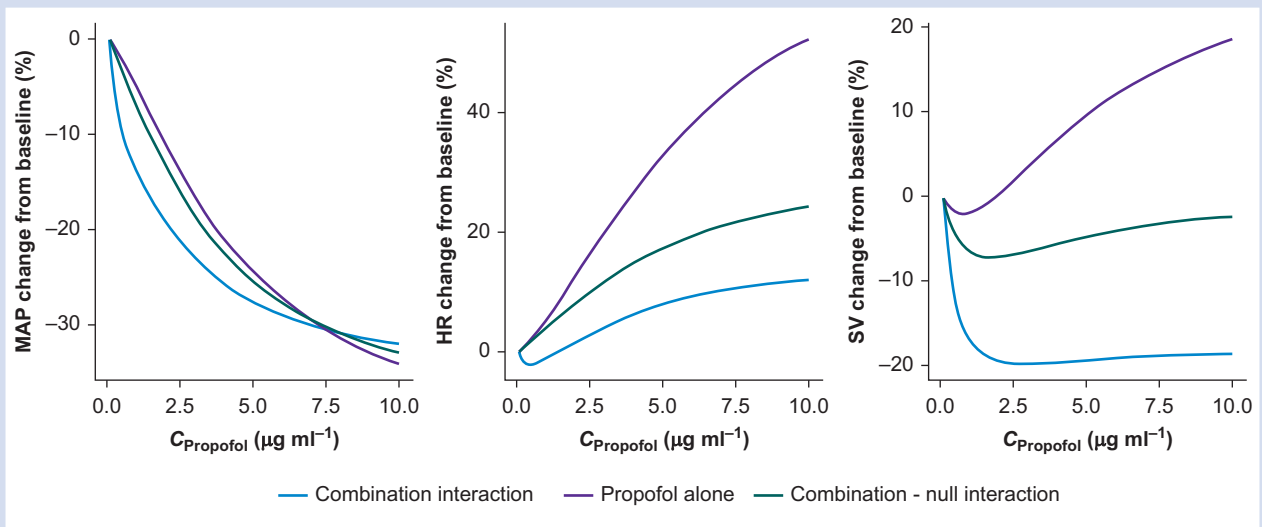
Fig 2. Predicted concentration–effect relationship (change from baseline) of MAP (left), HR (middle), and stroke volume (right) in a 35-yr-old individual for propofol alone (purple) and propofol combined with remifentanil 2 ng ml^{-1} predicted by the combination-null interaction model (green) or the combination interaction model (blue).
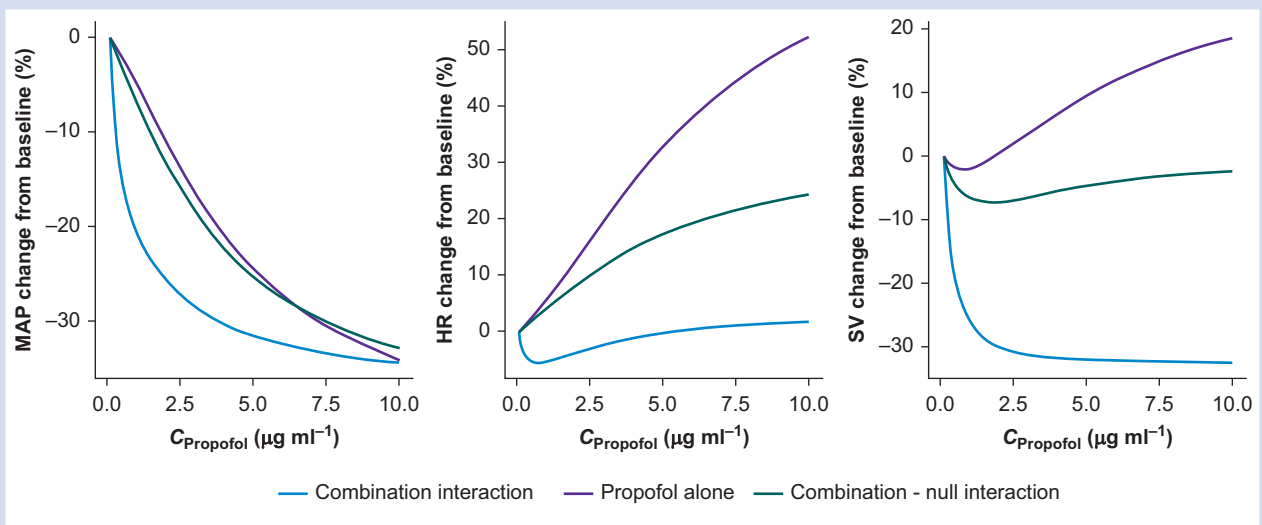

Fig 3. Predicted concentration–effect relationship (change from baseline) of MAP (left), HR (middle), and stroke volume (right) in a 35-yr-old individual for propofol alone (purple) and propofol combined with remifentanil 4 ng ml^{-1} predicted by the combination-null interaction model (green) or the combination interaction model (blue).

Lysakowski and colleagues[35] found that HR did not change significantly at a propofol target concentration of 0–4 µg ml^{-1} combined with remifentanil 6 ng ml^{-1}, which is comparable with our simulations. Our mechanism-based haemodynamic model can therefore potentially be used in clinical practice to predict how haemodynamic variables are influenced by propofol, remifentanil, and the combination.

To further support the clinical utility of the mechanism-based haemodynamic model, simulations were performed to understand the influence of titrating remifentanil on haemodynamics at a stable target concentration of propofol. We found that MAP changed along with the change in remifentanil concentration; however, the most significant change was caused by induction (Supplementary Fig. 5–1).

Simulations according to FDA drug label dosing[25,26] indicated that the interaction model was able to predict the median change in haemodynamic variables and the variability between individuals. The BSV for MAP, HR, and SV could
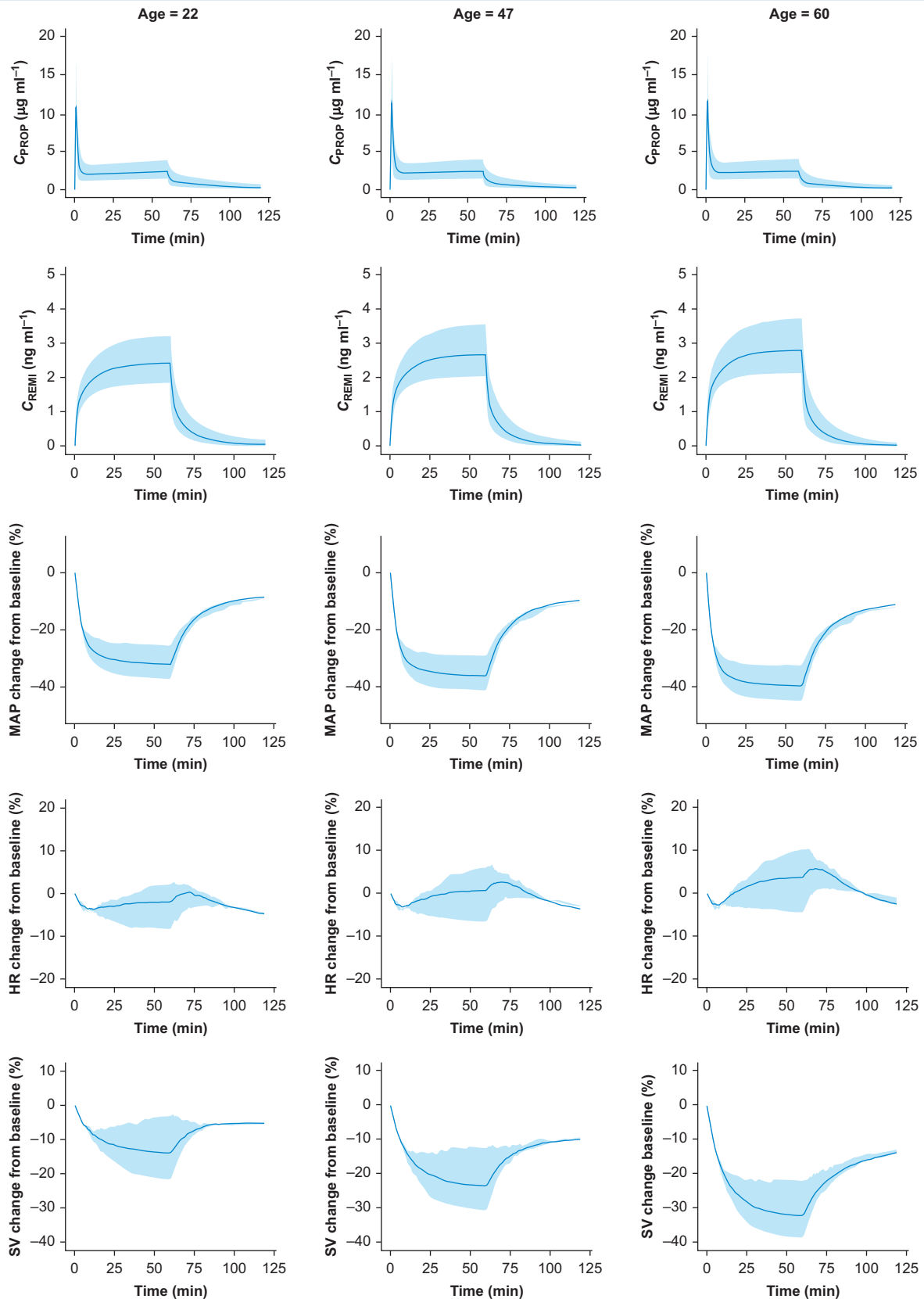
Fig 4. Predicted changes in propofol and remifentanil plasma concentrations and the relative changes in MAP, HR, and SV baselines during propofol combined with remifentanil infusion according to the US Food and Drug Administration drug label dosing for different ages. C_{PROP}, plasma concentration of propofol; C_{REMI}, plasma concentration of remifentanil; SV, stroke volume.

partially be explained by age. The propofol-induced decrease in SV was greater in older individuals, which caused a more pronounced decrease in MAP in the simulation (Fig. 4). This age effect is in agreement with the work by Südfeld and colleagues,[36] who showed that the risk for developing hypotension during general anaesthesia increases with age. Thus, to prevent severe haemodynamic side-effects, doses of general anaesthetics should be lower in older patients, which is in line with dosing recommendation in FDA propofol drug label.[25] Baseline measurements before surgery can potentially be used to enhance predictions of the model.

There are some limitations to this study. First, data from healthy subjects were used in the development of the mechanistic haemodynamic model of remifentanil and the interaction model. The ability to identify patient-specific covariates (concomitant medication, comorbidity status, etc.) reliably was therefore limited because of this homogenous population. Use of vasoactive medications, which are often used during induction of general anaesthesia, was not implemented in our model.[37] Therefore, the mechanism-based model should be restricted to conditions without vasoactive medication. Second, invasive BP was measured in the remifentanil-alone group, and noninvasive BP was measured in the propofol and combination groups. There is evidence that noninvasive MAP is in good agreement with invasive MAP.[38] However, for critically ill patients, noninvasive BP might not correlate with invasive arterial pressure measurements.[39] Based on our data, we could not detect any differences, however. Third, our goal was to inform anaesthesiologists of expected post-induction haemodynamic alterations, in particular post-induction hypotension. Our model was based on data from healthy volunteers and therefore lacks information on the impact of surgical factors. Drug-induced haemodynamic alterations frequently occur during induction of anaesthesia and when surgical stimuli are typically absent.[40] Nevertheless, the absence of information in the model on the effects of surgical stimulation limits the applicability of the model in these situations. Finally, the influence of typical patient-level confounders (anti-hypertensive medication, vasoactive drugs, frailty, etc.) on the model predictions has not been evaluated. Before clinical use of the model, the predictive performance of the model and the generalisability across patient groups should be prospectively validated.

In conclusion, a mechanism-based haemodynamic model was developed that quantifies the single-drug effects of propofol, remifentanil, and their combined administration in healthy volunteers. The effects of propofol and remifentanil cannot be described using the combination-null interaction model, as we identified an antagonistic interaction on HR, a synergistic interaction on stroke volume, and a mixed synergistic antagonistic interaction on mean arterial pressure that depends on the propofol concentration.

Authors' contributions

Study design: MMRFS, PJC
Data analysis: HS, JVK, DJE, PJC
Writing of first draft of paper: HS
Revision of manuscript: JVK, DJE, MMRFS, PJC

Declarations of interest

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Appendix A. Supplementary data

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