

Mechanism-based Pharmacodynamic Model for the Hemodynamic effects of Norepinephrine in Healthy Volunteers

Background and Objective

Intraoperation hypotension (IOH) is a common complication during general anesthesia (GA) and is associated with increased risk of adverse events [1,2]. IOH is closely monitored by continuously measuring blood pressure. Norepinephrine (NE) can be administered to restore vascular tone and blood pressure [3,4]. Despite routine use, the dose-exposure-response relationship of NE remains poorly quantified, and dosing relies largely on clinical experience. A previously published mechanism-based hemodynamic model was able to quantify the hemodynamic side effects induced by common drugs used in GA (i.e. propofol and remifentanyl). In this study, we aimed to evaluate whether a previously-developed mechanism-based model for the hemodynamic effects of GA could be enriched by including the hemodynamic effects of NE.

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Methods

A single-center, cross-over study was conducted in 36 healthy volunteers using a step-up NE dosing scheme (0.04, 0.08, 0.12, 0.16 and 0.20 µg-1 kg-1 min-1). Hemodynamic variables, including mean arterial pressure (MAP), heart rate (HR) and pulse pressure (PP) were collected. The mechanism-based model of Su *et al.* [5] was used as a foundation. The data were analyzed using the first-order conditional estimation method with interaction (FOCE-I) algorithm in NONMEM. Information from the Su model was incorporated into the current model by using a “frequentist prior” approach [6], which involves adding a penalty function based on the prior objective function value (OFV) derived from the current data.

Results

Final Mechanistic Model

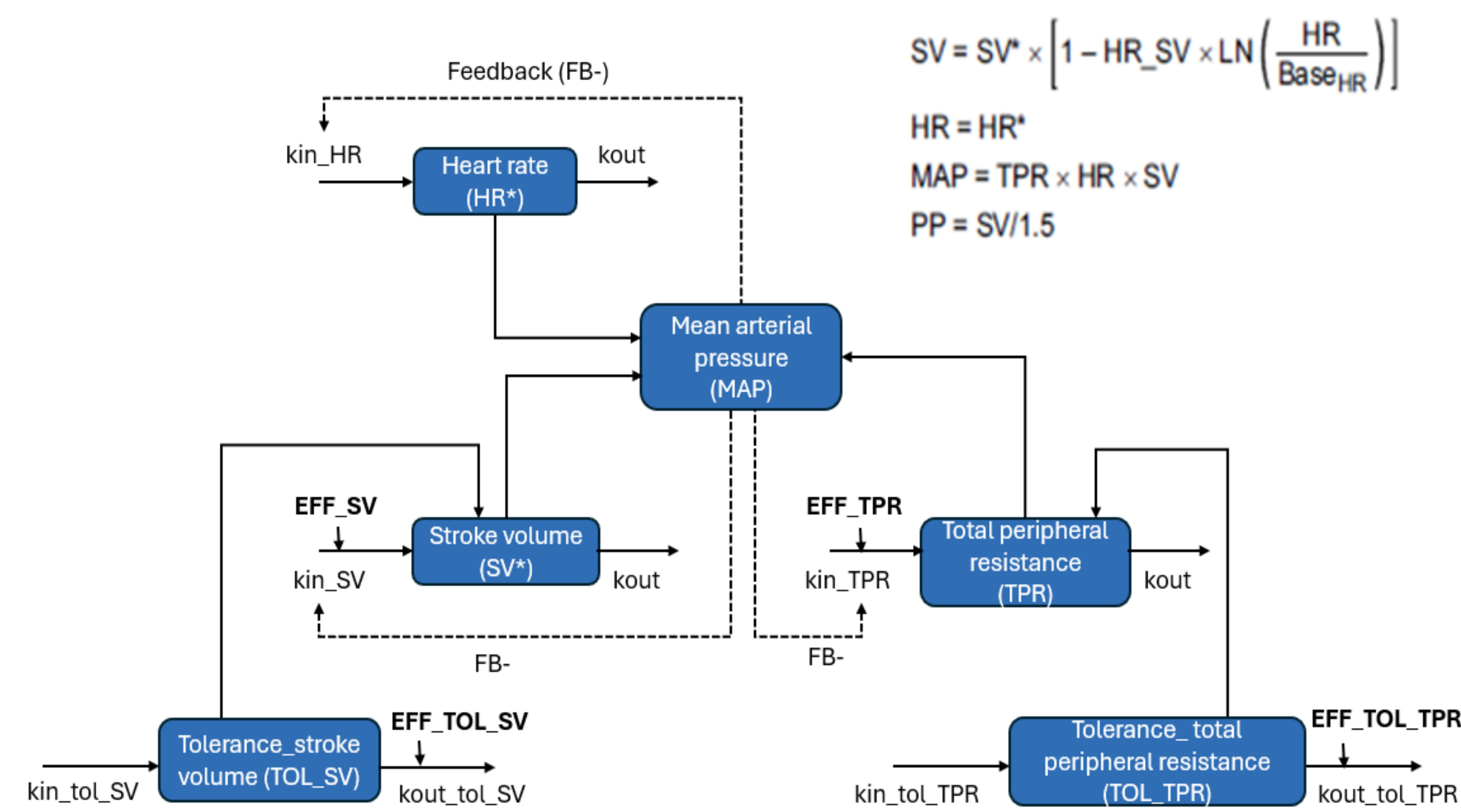


Fig.1. The structure of mechanism-based model which describes the dependency between MAP, HR, SV and TPR.

pvcVPC

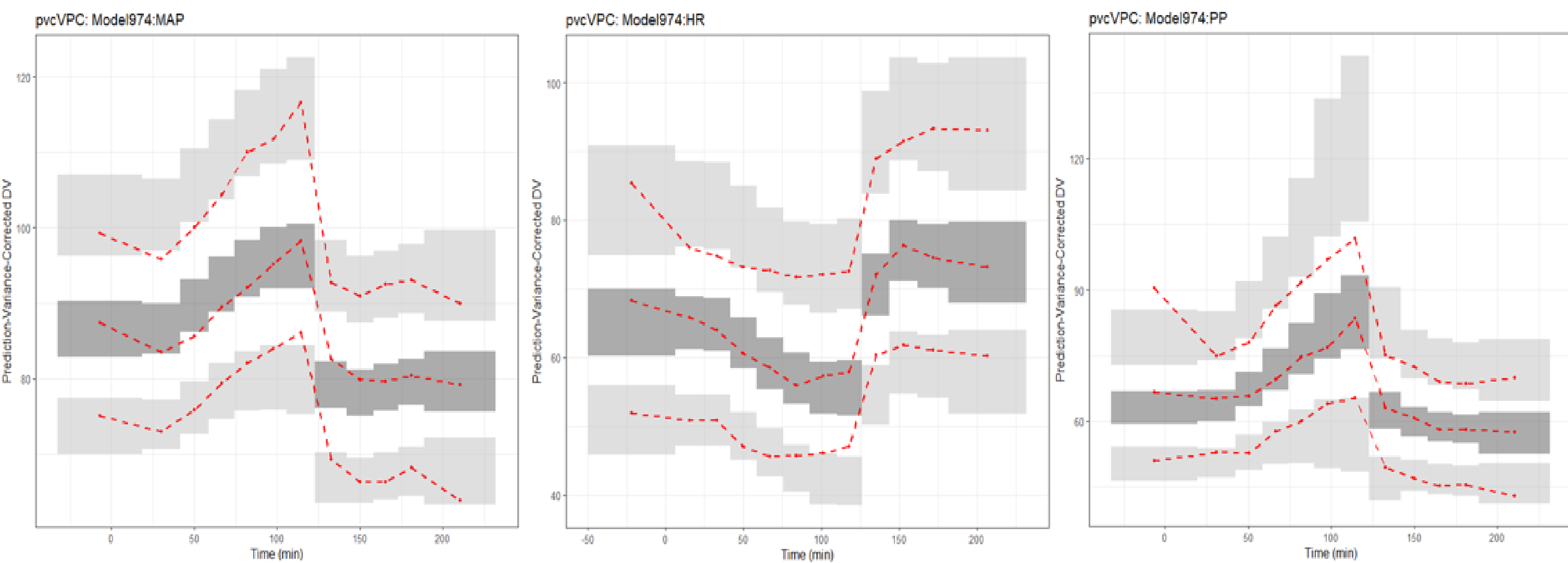


Fig.2 Prediction-Variance-Corrected visual predictive checks for MAP, HR and PP

- NE plasma concentration positively affected the production rate of TPR and SV and the effects were described by an exponential model.
- To account for the observed undershoot phenomenon in MAP and PP during the washout phase, a tolerance model was incorporated on the TPR (ΔOFV= -2787.3 points) and SV (ΔOFV= -2535.7 points).
- Changes in TPR, SV, and HR are shown in equations 1-6.

$$\frac{dT_{PR}}{dt} = k_{in_TPR} \cdot RMAP^{FB} \cdot e^{SL_{NE_TPR} \cdot CN} \cdot TOL_{TPR} - k_{out} \cdot TPR \quad (1)$$

$$\frac{dTOL_{TPR}}{dt} = k_{in_tol_TPR} - k_{out_tol_TPR} \cdot TOL_{TPR} \cdot e^{SL_{TOL_TPR} \cdot CN} \quad (2)$$

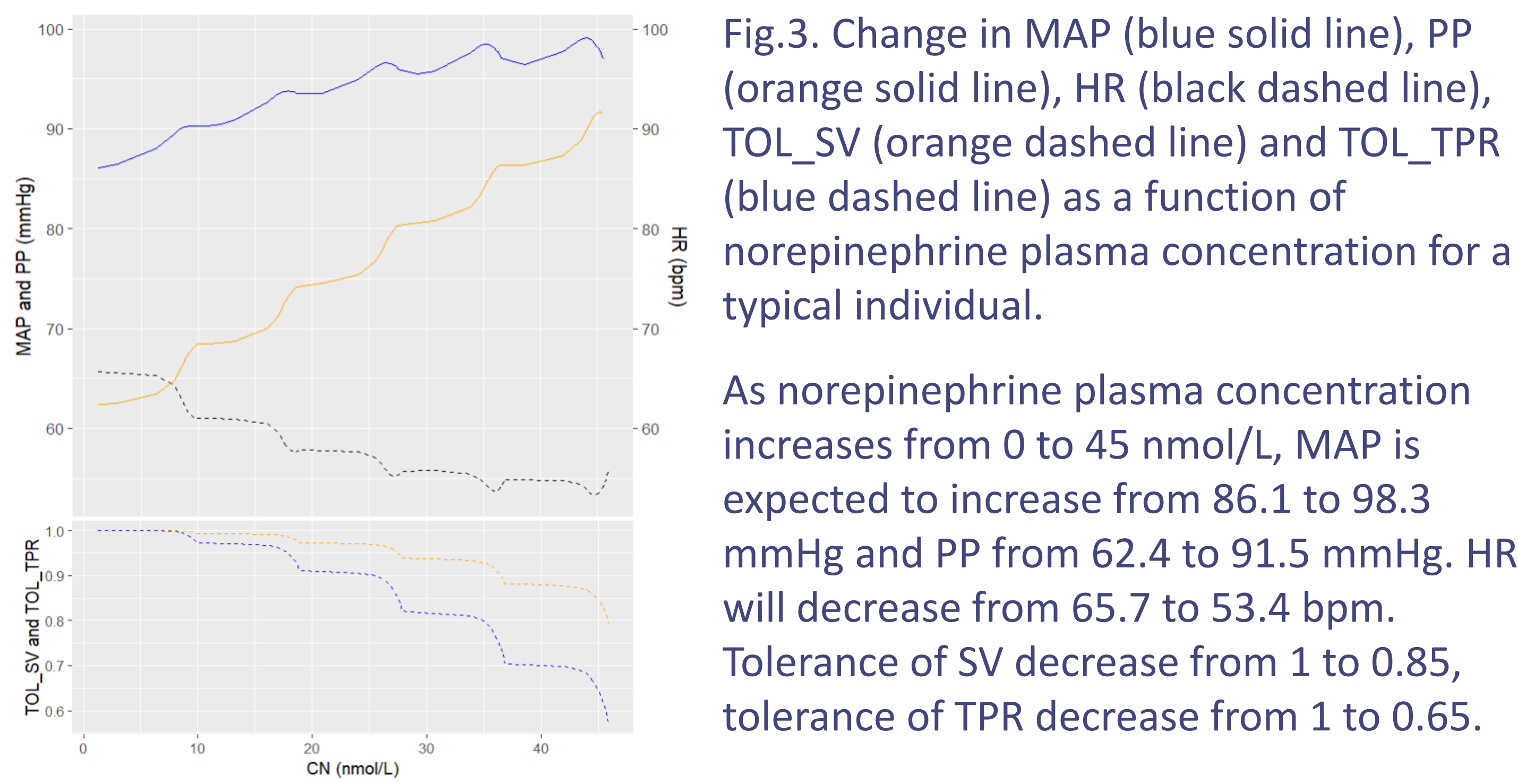
$$\frac{dSV^*}{dt} = k_{in_SV} \cdot RMAP^{FB} \cdot e^{SL_{NE_SV} \cdot CN} \cdot TOL_{SV} - k_{out} \cdot SV^* \quad (3)$$

$$\frac{dTOL_{SV}}{dt} = k_{in_tol_SV} - k_{out_tol_SV} \cdot TOL_{SV} \cdot e^{SL_{TOL_SV} \cdot CN} \quad (4)$$

$$\frac{dHR^*}{dt} = k_{in_HR} \cdot RMAP^{FB} - k_{out} \cdot HR^* \quad (5)$$

$$RMAP = \frac{HR \cdot SV \cdot TPR}{Base_{HR} \cdot Base_{SV} \cdot Base_{TPR}} \quad (6)$$

Exposure-Response relationship



Conclusions

The previously developed mechanism-based pharmacodynamic model was able to characterize the effects of norepinephrine on MAP, HR, PP in healthy volunteers. Future studies should aim at combining NE and GA hemodynamic drug effects before the model can be used to enhance the management of IOH in clinical practice.