



Mechanistic Modeling of Telmisartan Blood Pressure Lowering Effect in Human

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OBJECTIVES

In this study, a physioglocal PK-PD model with consideration of interactions between blood pressure, pulse pressure, heart rate, and total peripheral resistance is proposed. The objective is to improve upon the previous empirical models to achieve better predictive capabilities based on actual drug mechanisms.

METHODS

The data was acquired from a previous pharmacokinetic interaction study between rosuvastatin and telmisartan using randomized, open label, multiple-dose, 2x2 crossover design conducted in healthy volunteers in 2012 at Severance hospital, Seoul, Korea.

In that study, rosuvastatin 20 mg and telmisartan 80mg, each drug alone and in combination in crossover fashion, were given once daily for 6 days. Intensive blood sampling was performed on the last dosing day. Systolic and diastolic blood pressure and heart rate were measured as safety biomarkers during the study using digital blood pressure cuffs.

20 subjects who completed the monotreatment of telmisartan were used for PK/PD modeling and analysis.

1. Model Building

1) PK Model

Two compartment model was chosen as the basic disposition model, along which 1st order absorption model with absorption lag time best described the data. Weight has been incorporated into CL and V using the fixed allometric relationships as shown below:

$$CL = TVCL \cdot (WT/70)^{0.75} \quad (1)$$

$$V = TVV2 \cdot (WT/70) \quad (2)$$

No covariate was found to be statistically significant.

For model validation, the VPC result in figure 1 shows that most of the observations are within the 95% prediction interval.

2) Link Model

Telmisartan exerts drug effect by binding to angiotensin II receptor type 1 (AT1). Due to the difficulty estimating rate constants of drug binding and dissociation separately, the following differential equation was used:

$$\frac{d(C_b)}{dt} = k_{e0}(C_f - C_b) \quad (3)$$

C_f and C_b represent free and receptor-bound telmisartan concentration, respectively. The rate constant k_{e0} is an empirical parameter related to receptor-drug interaction.

3) PD Model

Mean arterial pressure (MAP) was chosen to be the dependent variable to be analyzed.

From physiology, assuming that mean venous pressure is negligible,

$$MAP = CO \cdot TPR \quad (4)$$

CO and TPR denote cardiac output and total peripheral resistance, respectively. Then, using the following relationships,

$$CO = SV \cdot HR \quad (5)$$

$$C = SV / PP \quad (6)$$

where SV, HR, C, and PP denote stroke volume, heart rate, compliance, and pulse pressure, respectively, Eq. (5) can be re-written as:

$$MAP = CTPR \cdot PP \cdot HR \quad (7)$$

where $CTPR = C \cdot TPR$

Equation (7) shows that MAP can be modeled as the product of CTPR and PP·HR, where CTPR can be represented as

$$CTPR = \frac{MAP}{PP \cdot HR} \quad (8)$$

(1) Model of PP and HR

Simultaneous fit of PP and HR were attempted where "slow drug effect" due to volume loss and decreased CO caused by telmisartan's natriuretic effect was incorporated as an I_{max} type inhibition function on turnover rate of PP as follows:

$$\frac{d(PP_{wc})}{dt} = k_{in,PP} \cdot \left[1 - \frac{C_b}{IC_{50,PP} + C_b} \right] - k_{out,PP} \cdot PP_{wc} \quad (9)$$

Assuming that phases of diurnal rhythm of PP and HR are synchronized, circadian rhythm was incorporated.

$$PP = PP_{wc} \cdot (1 + CIRC) \quad (10)$$

$$HR = HR_{wc} \cdot (1 + CIRC) \quad (11)$$

CIRC denotes a circadian rhythm including two oscillators with periods 12 and 24 h.

(2) Model for CTPR

Considering that vessel constriction and dilatation is governed by cytosolic calcium concentration,

$$\frac{d(Ca^{2+})}{dt} = k_{in} - k_{out}Ca^{2+} \quad (12)$$

Since the action mechanism of angiotensin II is to increased cytosolic Ca^{2+} , the binding of telmisartan to AT1 receptor will affect turnover of cytosolic Ca^{2+} , resulting in vasodilation, which can be regarded as "rapid drug effect". Thus, assuming TPR is approximately directly proportional to cytosolic Ca^{2+} level and the time course of CTPR follows that of TPR with C being assumed to be constant over the observation time, CTPR can be described as,

$$\frac{d(CTPR_{wc})}{dt} = k_{in,CTPR} \cdot \left[1 - \frac{C_b}{IC_{50,CTPR} + C_b} \right] - k_{out,CTPR} \cdot CTPR_{wc} \quad (13)$$

Since it is known that TPR has a circadian rhythm in the mirror image of the other cardiovascular indices, a circadian rhythm was incorporated into CTPR as follows:

$$CTPR = CTPR_{wc} \cdot (1 - MULT \cdot CIRC) \quad (14)$$

(3) Model for feedback

Feedback on HR was incorporated into HR as follows:

$$\Delta MAP = \frac{MAP - MAP_0}{MAP_0} \quad (15)$$

$$\frac{dHR_{wc}}{dt} = k_{in,HR} \cdot \left[\frac{1}{1 + K_f \Delta MAP} \right] - k_{out,HR} \cdot HR_{wc} \quad (16)$$

In the above equations, Δ MAP is used as the driving force of negative feedback, with MAP₀ being the baseline MAP, and K_f is the proportionality feedback constant

2. Model Implementation

Model building procedure for MAP proceeded sequentially by first obtaining circadian, turnover rate and drug effect parameters by modeling PP and HR data together, and then obtaining turnover rate, drug effect and MULT parameters for CTPR data, and finally obtaining baseline and feedback parameters by modeling PP, HR and CTPR data all together. In doing so, fixed-effect model parameters which were not estimated were fixed at their empirical Bayesian estimates obtained at the previous step, whereas random effect parameters were all estimated anew, with correlation between HR, PP, and TPR being taken into account to avoid unrealistic combination of parameters during simulation. The VPC of the final model is shown in figure 2.

3. Analysis Software

All model parameters were estimated using NONMEM software version 7.3, with PsN version 4.2 being used for summarizing data, stepwise covariate model building, and performing VPCs. R (RStudio) and MATLAB R2013a were used for additional data exploration, manipulation, and simulation.

RESULTS

Table 1. Parameter estimates of the final PD model

Parameter*	Population estimate (%RSE)
Structural Parameter	
CTPR ₀	0.030 (3.21%)
HR ₀ (/min)	67.7 (2.84%)
PP ₀ (mmHg)	47.74 (1.99%)
IC50 _{CTPR} (ng/mL)	1,110 (49.74%)
IC50 _{PP} (ng/mL)	3,238 (144.1%)
Keo (/h)	0.12 fix
Kout _{PP} (/h)	0.005 (166.8%)
Kout _{CTPR} (/h)	0.127 (30.66%)
AMP1 _(24 h)	0.059 (17.61%)
PHASE1 _(24 h) (h)	14.38 (7.12%)
AMP2 _(12 h)	0.019 (39.11%)
PHASE2 _(12 h) (h)	9.54 (9.06%)
Admission effect	0.035 (67.26%)
Variance Parameter	
CV _{CTPR0} (%)	13.19 (20.56%)
CV _{HR0} (%)	12.62 (14.34%)
CV _{PP0} (%)	7.30 (25.78%)
CV _{PHASE1 or 2} (%)	12.52 (34.28%)
ρ _{CTPR0-HR0}	-0.77
ρ _{CTPR0-PP0}	-0.47
ρ _{HR0-PP0}	-0.02
Residual variability	
CV _{residual_HR} (%)	7.25 (9.88%)
CV _{residual_PP} (%)	15.88 (6.26%)
CV _{residual_CTPR} (%)	6.70 (6.38%)

* CTPR₀, HR₀ and PP₀ denote baseline values of CTPR, HR and PP, respectively

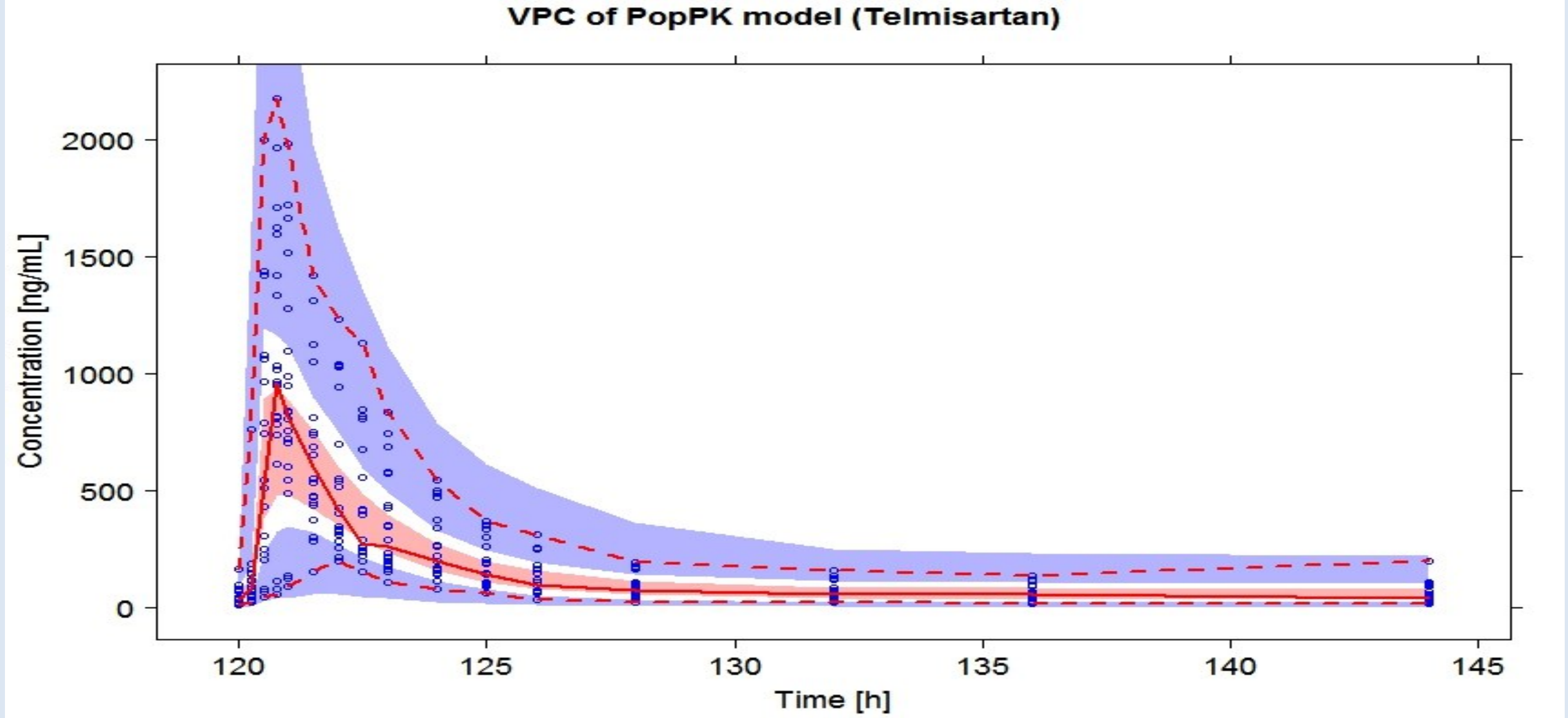


Figure 1. VPC of the final PK model (Red line: 2.5%, 50%, and 97.5% of observations, Red shaded area: 90% CI of 50% of population predicted values, Blue shaded area: 90% CI of 2.5% and 97.5% of population predicted values)

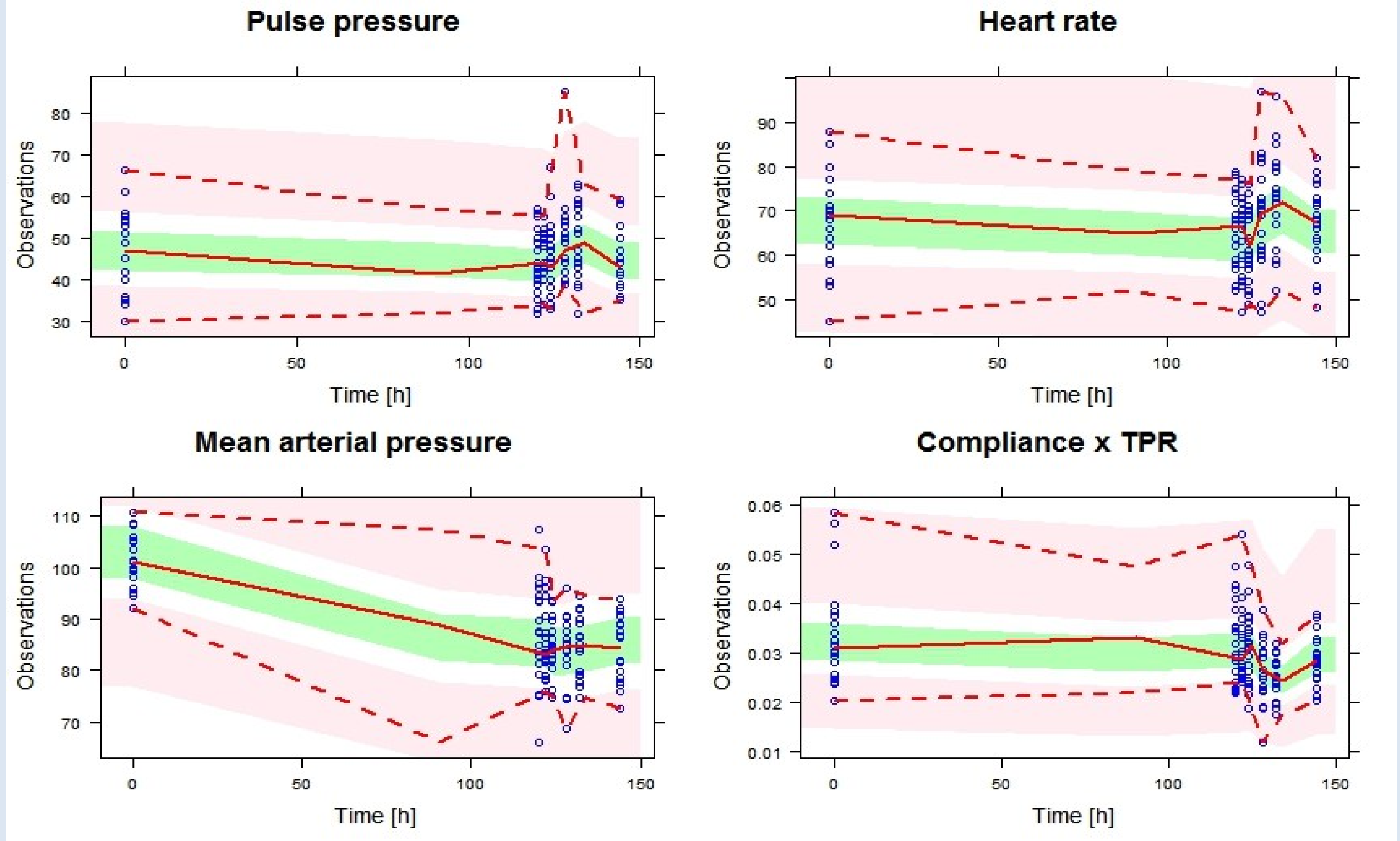


Figure 2. VPC of the final PD model (CI of 2.5%, 50%, and 97.5% predictive quantiles in colored bands, 2.5%, 50%, and 97.5% quantiles of observations shown as red lines).

CONCLUSIONS

This work demonstrated the feasibility of using a non-invasive cardiac index (HR) in deriving a mechanistic model of telmisartan's blood pressure lowering effect in human. The developed model can be similarly applied to antihypertensive drugs other than ARBs

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