

Deciphering the mechanisms of drug effects on cardiovascular system through semi-mechanistic modeling of preclinical telemetry data: a validation study

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Abstract

Preclinical telemetry data on heart rate (HR) and mean arterial pressure (MAP) was used to assess the ability of semi-mechanistic model by Snelder et al.² to elucidate the primary and secondary hemodynamic effects of the drugs with known mechanism of action.

Introduction

- Model-based analyses of preclinical telemetry data provide important basis for the preclusion of adverse cardiovascular (CV) effects in clinical development¹.
- Snelder et al. has developed an integrative model of the CV system to distinguish between the drug-induced response and subsequent physiological feedback of the hemodynamic parameters².

Objective

The aim of this work is to validate the model using limited telemetry data for compounds with known mechanism of action, previously unused in model development.

Methods

Glycopyrrolate	Vehicle	0.03 mg/kg	0.1 mg/kg	0.5 mg/kg
			0.05 mg/kg	
Nifedipine	Vehicle		3 mg/kg	30 mg/kg
		2 mg/kg	2.5 mg/kg	3 mg/kg
Atenolol	Vehicle		10 mg/kg	100 mg/kg
		1 mg/kg	5 mg/kg	
Clonidine	Vehicle		0.1 mg/kg	
		0.06 mg/kg	0.125 mg/kg	0.25 mg/kg

- Internal data - PD data (MAP and HR)
- External data - PK data

Figure 1. Data used in the analysis

(internal data - 8 Wistar-Kyoto rats; external data - published rat PK data (9 studies))

- The model in question consists of 16 parameters and three turnover equations: HR, stroke volume (SV) and total peripheral resistance (TPR), along with circadian variations, handling effects, feedbacks from MAP and SV (Fig. 2).
- Sequential modeling approach was used: first, PK parameters were identified; then, circadian variations and handling effects were introduced; finally, the drug effect was quantified on different sites of action, individually or in combinations. Optimal structural and statistical models were selected based on minimal AIC, goodness of fit plots and estimated parameter precision.
- Monolix (version 2020R1) and R software (version 4.0.2) were used for model development, evaluation and simulations.

Table 1. Parameters of the PK model

	Glycopyrrolate		Nifedipine		Atenolol		Clonidine	
	Name	Value (RSE, %)	Name	Value (RSE, %)	Name	Value (RSE, %)	Name	Value (RSE, %)
Parameters	Vc, L/kg	0.23 (3.96)	Fbio	0.33 (0.21)	Fbio	0.88 (0.51)	Fbio	0.61 (12.7)
	CL, L/kg/h	3.44 (0.83)	ka, h ⁻¹	2.45 (18.3)	ka, h ⁻¹	0.16 (4.01)	ka, h ⁻¹	2.88 (18)
	Vp, L/kg	4.5 (3.2)	Vc, L/kg	0.2 (0.61)	Vc, L/kg	0.41 (fixed)	Vc, L/kg	3.32 (8.53)
	Q, L/kg/h	2.92 (0.54)	CL, L/kg/h	0.23 (0.53)	CL, L/kg/h	2.51 (fixed)	CL, L/kg/h	1.42 (13.2)
			Vp, L/kg	0.63 (4.99)	Vp1, L/kg	0.62 (fixed)	Vp, L/kg	9.44 (7.98)
Route	Intratracheal, IV		Oral, IV		Oral, IV		Oral, IV	

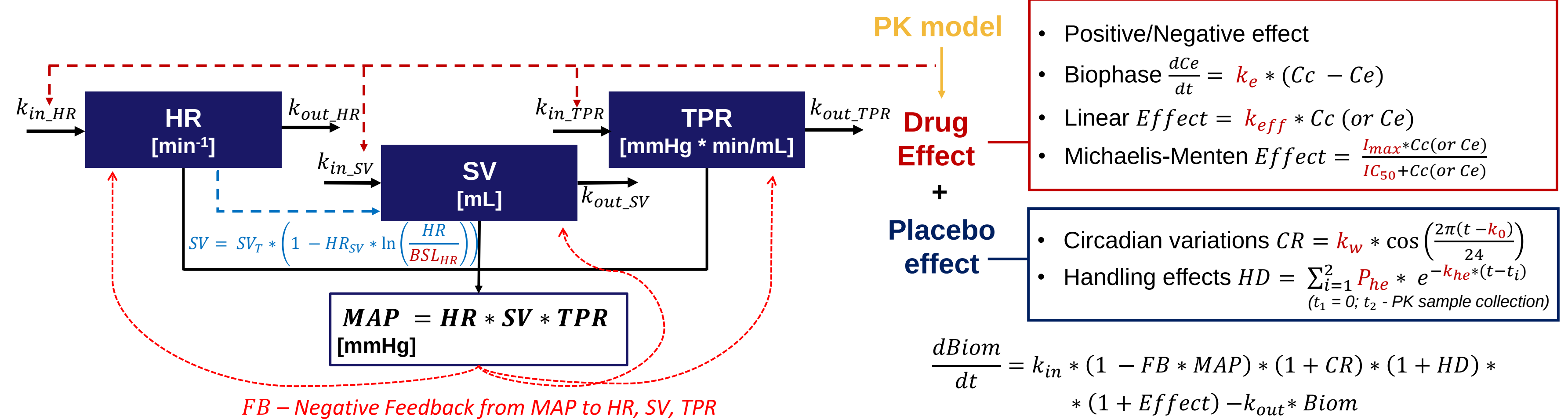


Figure 2. Semi-mechanistic model of CV system.

"Biom" represents HR, TPR or SV; Circadian variations introduced only on HR and TPR; Handling effects introduced only on HR; red colored parameters were estimated

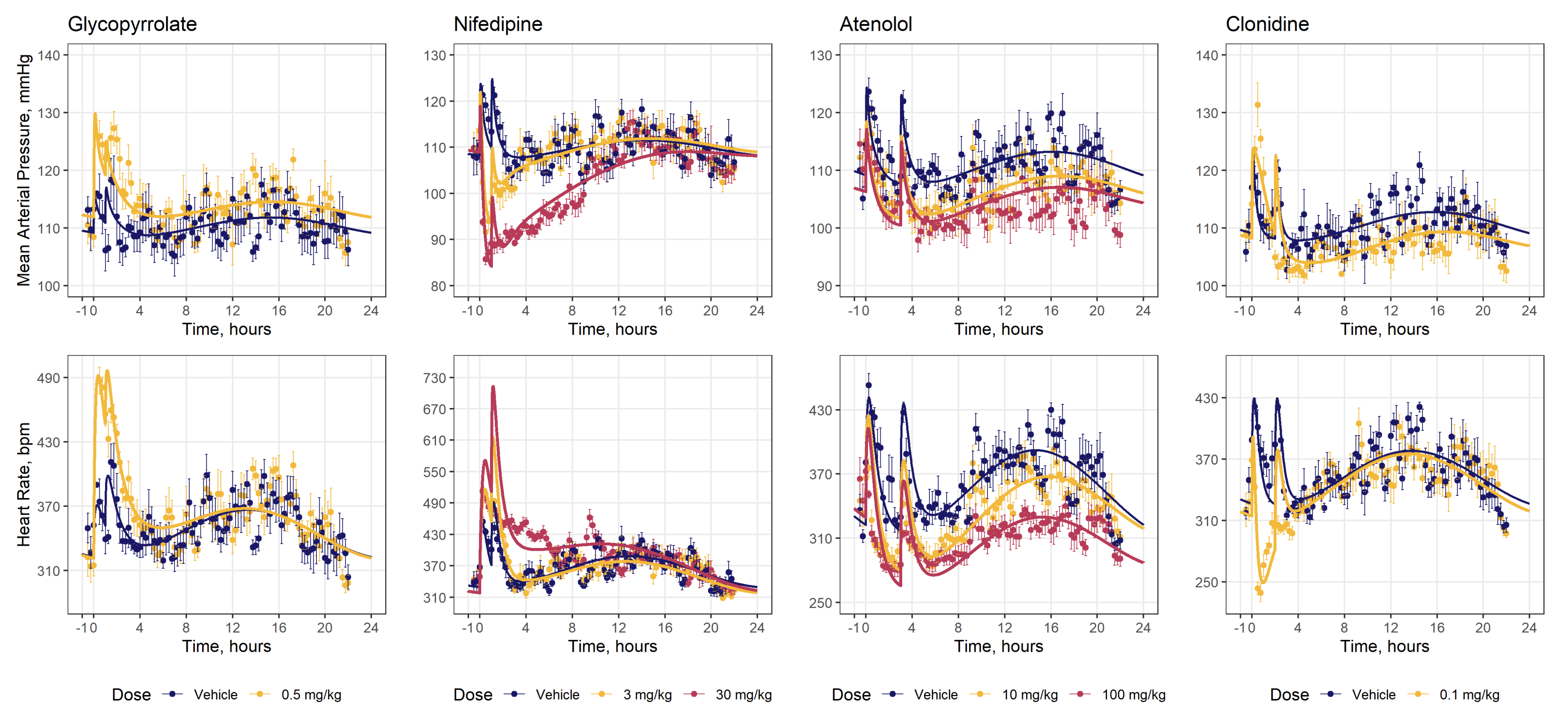


Figure 3. Observed and predicted changes over time in HR and MAP

Table 2. Drug effect parameters in the optimal models

Glycopyrrolate		Nifedipine		Atenolol		Clonidine	
Parameter	Value (RSE, %)	Parameter	Value (RSE, %)	Parameter	Value (RSE, %)	Parameter	Value (RSE, %)
k_e , h ⁻¹	1.11 (1.04)	I_{max_TPR}	0.62 (2.43)	I_{max_HR}	0.25 (6.24)	k_{eff_HR} , uM ⁻¹	-3.93 (31.3)
k_{eff_HR} , uM ⁻¹	3.17 (10)	IC_{50} , uM	1.93 (10.5)	IC_{50} , uM	0.41 (25.1)	k_{eff_SV} , uM ⁻¹	-30.37 (12.8)
						k_{eff_TPR} , uM ⁻¹	21.38 (10.9)

Table 3. Empirical and model-derived theoretical primary drug effects

Compound	Glycopyrrolate	Nifedipine	Atenolol	Clonidine
Expected empirical effect	HR ↑	TPR ↓	HR ↓ TPR ↓	HR ↓ TPR ↓ SV ↓
Model-derived effect	HR ↑	TPR ↓	HR ↓	HR ↓ TPR ↑ SV ↓

Results

- PK models were successfully developed (Table 1). Placebo and PD response was adequately described by the selected optimal integrative models (Fig. 3), with positive linear effect on HR for glycopyrrolate, Imax-type effect on TPR for nifedipine and on HR for atenolol, and negative linear effect on HR and SV and positive linear effect on TPR for clonidine (Table 2).
- Predicted primary effects for all compounds are in agreement with the empirical effects, except for clonidine: as an alpha-2 adrenoreceptor agonist, clonidine is expected to cause a decrease in HR and TPR leading to a decrease in MAP. However, in our study in conscious rats, clonidine increased MAP which cannot be described by a decline in HR and TPR (Table 3).

Conclusions

- The primary effects of four compounds (glycopyrrolate, clonidine, nifedipine, atenolol) on CV toxicity were identified based on rat HR and MAP data using the semi-mechanistic modeling.
- The general alignment of the primary drug effects predicted by the model with known empirical targets confirms the validity of the approach and sets a basis for translation of the model to other species.

References

- V. Sokolov, A. Sofronova, L. Stolbov, et al. Model-based analyses of preclinical telemetry data in support of decision-making in early drug development: an exemplar workflow.
- Snelder N, Ploeger BA, Luttringer O, et al. Drug effects on the CVS in conscious rats: separating cardiac output into heart rate and stroke volume using PKPD modelling. Br J Pharmacol. 2014 Nov;171(22):5076-92. doi: 10.1111/bph.12824.
- van Steeg TJ, Freijer J, Danhof M, de Lange EC. Pharmacokinetic-pharmacodynamic modelling of S(-)-atenolol in rats: reduction of isoprenaline-induced tachycardia as a continuous pharmacodynamic endpoint. Br J Pharmacol. 2007 Jun;151(3):356-66. doi: 10.1038/sj.bjp.0707234.