Population modeling of blood pressure: assessing clinically important factors for cardiovascular diseases

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Introduction

- Blood pressure (BP) exhibits diurnal variation with chronobiological rhythm (circadian) with an increase in the morning an decrease during the night
- Circadian processes are often analyzed using a Fourier approach, resulting in a sum of cosine functions
- These models fail to relate the obtained parameters (amplitude, acrophase) with important clinical features of the circadian rhythm, such as nocturnal dip and morning surge
- Patients with a small nocturnal dip or an increased morning surge are at higher risk to develop cardiovascular diseases or events (e.g. stroke) [1]

Objective

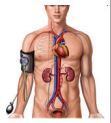
Development of a model

- to **describe the chronobiolocial rhythm** in systolic blood pressure (SBP) with **clinically relevant parameters** predictive for **cardiovascular events**
- to identify possible **covariates** as predictors for higher cardiovascular risk

Study Design

Baseline blood pressure

- 192 potentially mildly hypertensive patients
- Screening for inclusion into ROTATE study [2]
- 24h ambulatory SBP measurement at regular time intervals (15-30min)



Approach

I. **Fourier analysis** for the circadian (24h) and ultradian (12, 8, 6, …) harmonic cosine rhythms

II. **Reparameterisation** of the developed model

III. **Validation** of identified parameters with widely used features of circadian pattern of BP

IV. **Covariate analysis** with: Gender, ethnicity, age, BMI, cholesterol, LDL, HDL, creatinine, mean 24h SBP, diabetes, sodium intake, smoking, exercise single-nucleotide-polymorphisms (SNP's)

BP modelling

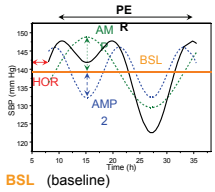
Reparameterised model

$$BP = BSL + AMP * \cos\left(\frac{2\pi(TIME + HOR)}{PER}\right) + AMP2 * \cos\left(\frac{2 * 2\pi(TIME + HOR)}{PER}\right)$$

$$AMP = BSL - NAD + AMP2$$

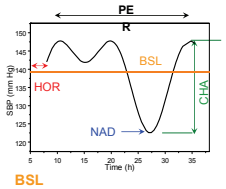
$$AMP2 = \frac{1}{3}(BSL - NAD) - \frac{4}{9}CHA - \frac{2}{9}\sqrt{6CHA * (NAD - BSL) + 4CHA^2}$$

Baseline model



BSL (baseline)
PER (period=24h)
HOR (horizontal displacement)
AMP (amplitude 24h)
AMP2 (amplitude 12h)

Reparameterised model



BSL
PER
HOR
CHA (change night → morning)
NAD (nadir night)

Method: NONMEM v7 with FOCE interaction method

Results

- **The reparameterised model adequately describes the SBP (figure 1) with a precise estimation of clinically relevant parameters (Table 1)**
- **The estimated model parameters show good correlation with clinically important features such as nocturnal dip, mean SBP day and morning surge.**
- **Ethnicity was identified as covariate on the parameter CHA (change night to morning), related to the morning surge (Table 3).**

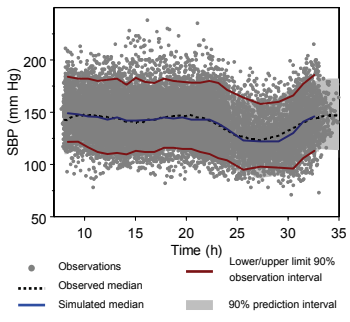
I. Reparameterised model

- Compared with baseline model

No difference in objective function (MVOF) was observed between the baseline and reparameterised model, which shows that the reparameterisation is successful

- VPC

Figure 1: Visual Predictive Check (VPC) of 24h baseline profile of SBP, based on 100 simulations



- Parameter estimates

Table 1: population parameter obtained from fitting the SBP measurements with the reparameterised model

Parameter	Unit	Value	SE*	CV(%)*	LLCI*	ULCI*
		Fixed effects				
BSL (baseline SBP)	mm Hg	139	1.12	0.8	137	141
NAD (nadir)	mm Hg	122.3	17.1	14.1	88.7	155.9
PER (period)	h	24 FIX				
HOR (horizontal shift)	h	8.8	0.1	1.2	8.6	9.0
CHA (change night-day)	mm Hg	25.4	1.0	4.0	23.4	27.4
		Random effects (inter-individual variability (IIV)				
$\omega^2_{BSL\ (IIV)}$		0.0123	0.00126	10.2	0.00983	0.0148
$\omega^2_{NAD\ (IIV)}$		0.024	0.00363	15.1	0.0169	0.0311
$\omega^2_{HOR\ (IIV)}$		0.238	0.0306	12.9	0.178	0.298
$\omega^2_{CHA\ (IIV)}$		4.18	0.646	15.5	2.91	5.45
$\omega^2_{CHA\ (IIV)} \times \omega^2_{NAD\ (IIV)}$		-0.326	0.0985	-30.2	-0.519	-0.133
		Random effects (residual error)				
σ^2_+ (additive)		142	4.08	2.87	134	150

- η-shrinkage: < 20.0%
- ε-shrinkage: 2.3%

The reparameterised model shows an adequate description of the 24h baseline SBP with precise parameter estimates

II. Validation parameters with literature

For 49 randomly selected subjects the parameter estimates were compared with clinically relevant features for cardiovascular events, as defined in literature [1, 3]:

Feature	Definition		Model Parameter
Mean Day:	average SPB during day	⟷	BSL
Min. night:	average of 3 lowest SBP during night	⟷	NAD
Nocturnal dip:	ratio Min.night/mean day	⟷	NAD/BSL
Morning surge:	min. night - morning peak	⟷	CHA

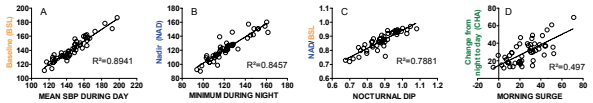


Figure 2: A strong correlation was observed between BSL vs. Mean Day (A), Nadir vs. Min. Night (B), NAD/BSL vs. Nocturnal dip (C). The correlation between CHA vs. Morning Surge is less evident (D).

The morning surge is defined as the difference between Min.night and the average SBP during 2h post self reported rise. A clear benefit of the model is shown here since the parameter CHA is estimated using the full 24h profile (Figure 2D)

III. Covariate analysis

Table2: The developed model was used to screen for possible predictors in this heterogeneous study population. Based on a stepwise covariate analysis (forward inclusion, backward deletion), the covariate of **ethnicity** was found on the parameter **CHA**

	Population estimate (+95% CI)		
Parameter	Dutch Caucasian	South Asian	Blacks
CHA	31 (27-35)	28 (23-33)	22 (20-24)

Black people show a significant lower CHA

Conclusions and perspectives

- based on a 24h ambulatory BP measurement the reparameterised model can be used in clinical practice to assess the morning surge, nocturnal blood pressure and nocturnal dip, all associated with cardiovascular events
- The proposed model allows an extended covariate screening including more patients to identify besides ethnicity other risk factors for CV events
- Moreover this baseline BP model can form the basis for the development of a PK-PD model to evaluate the drug effect of anti-hypertensive drugs

References

[1] Kario, K., Hypertension, 2010. 56(5): p. 765-73. [2] van Rijn-Bikker, P.C. et al., Am J Hypertens, 2009. 22(12): p. 1295-302. [3] Hansen, T.W. et al. Hypertension 2011;57(1): p.3-10