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 and 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 chronobiological 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]
- 24 ambulatory BP 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)

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 (MOVF) 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](image)

![Table 1: population parameter obtained from fitting the SBP measurements with the reparameterised model](table)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MOVF</th>
<th>BLS (baseline)</th>
<th>PER (period=24h)</th>
<th>NAD (Nadir)</th>
<th>BSL (Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. night</td>
<td>0.60</td>
<td>0.21</td>
<td>0.26</td>
<td>0.17</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean day</td>
<td>0.70</td>
<td>0.32</td>
<td>0.37</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>MAX. night</td>
<td>0.80</td>
<td>0.32</td>
<td>0.40</td>
<td>0.27</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean day</td>
<td>0.90</td>
<td>0.36</td>
<td>0.45</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>MIN. (night)</td>
<td>-0.20</td>
<td>-0.04</td>
<td>-0.05</td>
<td>-0.06</td>
<td>-0.05</td>
</tr>
<tr>
<td>Mean day</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>MAX. (night)</td>
<td>0.20</td>
<td>0.09</td>
<td>0.10</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean day</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

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

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

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)

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]

<table>
<thead>
<tr>
<th>Feature</th>
<th>Definition</th>
<th>Model Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Day</td>
<td>average SBP during day</td>
<td>BLS</td>
</tr>
<tr>
<td>Min. night</td>
<td>average of 3 lowest SBP during night</td>
<td>NAD</td>
</tr>
<tr>
<td>Nocturnal dip</td>
<td>ratio Min.night/day</td>
<td>NAD/BLS</td>
</tr>
<tr>
<td>Morning surge: min. night – morning peak</td>
<td>CHA</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 3: Population estimate (+95% CI)](image)

The proposed model allows an extended covariate screening including more patients to identify besides ethnicity other risk factors for CV events

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