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Original Article

A cyclic fluctuation model for 24-h ambulatory blood pressure monitoring in Chinese patients with mild to moderate hypertension

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Aim: The conventional method for analyzing 24-h ambulatory blood pressure monitoring (24-h ABPM) is insufficient to deal with the large amount of data collected. The aim of this study was to develop a novel cyclic fluctuation model for 24-h ABPM in Chinese patients with mild to moderate hypertension.

Methods: The data were obtained from 4 independent antihypertensive drug clinical trials in Chinese patients with mild to moderate hypertension. The measurements of 24-h ABPM at the end of the placebo run-in period in study 1 were used to develop the cyclic fluctuation model. After evaluated, the structural model was used to analyze the measurements in the other 3 studies. Models were fitted using NONMEM software.

Results: The cyclic fluctuation model, which consisted of 2 cosine functions with fixed-effect parameters for rhythm-adjusted 24-h mean blood pressure, amplitude and phase shift, successfully described the blood pressure measurements of study 1. Model robustness was validated by the bootstrap method. The measurements in the other 3 studies were well described by the same structural model. Moreover, the parameters from all the 4 studies were very similar. Visual predictive checks demonstrated that the cyclic fluctuation model could predict the blood pressure fluctuations in the 4 studies.

Conclusion: The cyclic fluctuation model for 24-h ABPM deepens our understanding of blood pressure variability, which will be beneficial for drug development and individual therapy in hypertensive patients.

Keywords: blood pressure; 24-h ambulatory blood pressure monitoring; cyclic fluctuation model; NONMEM; hypertension; Chinese patients

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Introduction

Twenty-four-hour ambulatory blood pressure monitoring (24-h ABPM) is an important indicator in hypertension diagnosis and the evaluation of the effects of antihypertensives[1–3]. Multiple measurements of blood pressure within a day using 24-h ABPM can be relatively objective and can truly reflect the patient's blood pressure levels compared to casual blood pressure measurement. Thus, this method can diagnose white coat hypertension, masked hypertension and morning hypertension. Moreover, it also facilitates understanding the circadian rhythm of blood pressure and fluctuation characteristics. Recently, 24-h ABPM has been regarded as a confirmatory method for the diagnosis of hypertension in the British hypertension guidelines[4]. In addition, 24-h ABPM is also indicated to predict target organ damage and the prognosis of cardiovascular disease patients. It has been confirmed that 24-h average blood pressure is more related to target organ damage and the prognosis of hypertension than casual blood pressure measurement[5–7].

The ideal antihypertensive drug should lead to a steady decline in blood pressure over an entire 24-h period. According to the guiding principle for clinical trials of new antihypertensive drugs by the Chinese SFDA, an ABPM study conducted in a certain number of hypertensive patients must be included as a part of new antihypertensive drug clinical trials[8]. Although many 24-h ABPM studies have been conducted in China, the commonly used analytic method for 24-h ABPM is still insufficient with regard to the large amount of acquired data. Some cyclic fluctuation models for 24-h ABPM have been developed in non-Chinese populations[9, 10]. How-

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ever, higher nighttime blood pressure has been observed in Chinese patients compared with non-Chinese patients[11, 12]. In the Chinese population, a high-salt diet and gene polymorphisms may also influence the pattern of blood pressure changes[13, 14]. It is important to understand and describe the cyclic fluctuations of blood pressure in Chinese hypertensive patients. The goal of this study was to develop a cyclic fluctuation model for blood pressure in patients with mild to moderate hypertension in 4 antihypertensive drug clinical studies in China. This model will be beneficial for antihypertensive therapy in clinical practice and new drug development.

Materials and methods

Data sources and study design

The 24-h ABPM data were collected from 4 antihypertensive drug clinical trials that were conducted in accordance with the Declaration of Helsinki. Patients were enrolled in these 4 studies if they were 18–75 years of age with mild or moderate hypertension (mean sitting systolic BP/mean sitting diastolic BP, mild: 140–159/90–99 mmHg, moderate: 160–179/100–109 mmHg)[15]. The major exclusion criteria included significant cardiovascular, hepatic, and renal disease and concomitant type 1 diabetes or uncontrolled type 2 diabetes, childbearing potential, current use of anticonvulsant or antidepressant therapy, and history of drug abuse. All subjects signed an informed consent before any study-related procedures were performed.

The 4 studies included a 2-week placebo run-in period, followed by an 8-week, open-label antihypertensive treatment period. Drugs (placebo or antihypertensive agents) were administered orally between 7 and 10 AM once daily. On study visit days, patients were instructed not to take their study medication until the assessments were completed. Twenty-four-hour ABPM was used at the end of each period. The blood pressure measurements in all studies were performed every 15 min from 8 AM to 10 PM and every 30 min from 10 PM to 8 AM with an Ambulatory Blood Pressure Monitor (SunTech Medical Instruments, Raleigh, NC, USA). The blood pressure fluctuation model in this study was based on the 24-h ABPM data collected at the end of the run-in period. Patient demographics and the description of 24-h ABPM at the end of the placebo run-in period are shown in Table 1.

Modeling and validation

Structural model

The blood pressure fluctuation model was based on a model of the 24-h ABPM profile without drugs present that was previously described by Hempel[9, 10]. The original model for the ABPM measurements was represented as follows:

$$BP_k(t)=Base_k \cdot \{1+\sum_{i=1}^{n} A_{ik} \cdot \cos[\frac{i \cdot \pi \cdot (t-PHS_{ik})}{0.5}]\}$$

In this equation, k=1 is systolic blood pressure, k=2 is diastolic blood pressure, $BP_k(t)$ is the blood pressure as a function of t (the unit of t is day), $Base_k$ is the rhythm-adjusted 24-h mean, A_{ik} is the amplitude of the cosine terms, and PHS_{ik} is the parameter for phase shifts of the cosine terms. The number of cosine functions (n) was selected based on the minimum objective function values (OFVs) and diagnosis plots. Additional forms of the original model were also tested.

Two independent sets of parameters were used to fit the fluctuation models for diastolic and systolic blood pressure measurements, respectively. Based on a graphical inspection of the raw data, equal values of phase-shift parameters (*ie*, $PHS_{i1}=PHS_{i2}$) for both diastolic and systolic blood pressure measurements were also used. Model selection was based on the goodness-of-fit plots, estimates and standard errors of the population parameters, and OFVs.

Covariate model selection

The influence of covariates was evaluated after the structural model was developed. The covariates considered in the BP model parameters were demographic factors [gender, age, weight, body mass index (BMI)]. Diagnostic plots of possible covariates versus the inter-individual variabilities were first

Table 1. Patient demographics and description of the data sets used.

	Study 1	Study 2	Study 3	Study 4
No of patients	38	42	25	29
Sex				
Male	17	22	16	15
Female	21	20	9	14
Age (year)*	51.6±7.83 (35, 69)	50.9±7.91 (35, 69)	51.0±12.3 (28, 72)	48.8±9.79 (36, 72)
Weight (kg)*	65.5±9.27 (45, 85)	73.9±10.8 (55, 95)	65.9±10.4 (46, 90)	72.9±11.0 (52, 105)
Height (cm)*	165±8.05 (152, 183)	168±7.30 (150, 180)	164±7.71 (149, 183)	167±8.26 (150, 183)
BMI (kg/m^2)*	24.0±2.91 (17.6, 28.7)	26.2±2.80 (20.8, 30.0)	24.5±2.72 (18.4, 29.7)	26.0±2.75 (23.0, 30.3)
Average 24-h SBP (mmHg)*	141±15.6 (120, 175)	145±16.1 (122, 194)	139±15.1 (125, 165)	137±13.9 (118, 157)
Average 24-h DBP (mmHg)*	90.4±10.2 (80, 119)	92.8±10.8 (80, 124)	90.2±10.5 (80, 117)	90.2±9.8 (81, 103)
No of SBP measurements	2110	2927	2346	1687
No of DBP measurements	2110	2927	2346	1687

*Mean±SD (minimum and maximum values in parentheses). Average 24-h blood pressures were directly read from the automatic analysis.

used to screen for relevant covariates that could influence the individual parameters obtained from the structural model. The screened covariates were evaluated by changes of the OFV. Assuming that the differences in the OFVs had a chi-square distribution, a decrease in OFV greater than 3.84 from the structural model (P<0.05) was used for stepwise forward inclusion. The full model was built by introducing all significant covariates. Subsequently, the final model was developed using a stepwise backward elimination procedure. Covariates remained in the final model when the elimination of the variable caused a significant increase in OFV greater than 6.63 compared to the full model (P<0.01). Goodness-of-fit graphs were also applied for model evaluation.

Continuous covariates were standardized to their mean values and were modeled as an exponential function by the following equation:

$$\theta=\theta_T(\frac{cov}{Mean_{cov}})^{\theta cov}$$

Categorical variables were modeled using a proportional change model as shown:

$$\theta=\theta_T(cov_1+\theta_{cov}\,cov_2)$$

where cov_1 and cov_2 were indicator variables set equal to '1' to denote the ith covariate value and '0' otherwise, θ_T was the model parameter for cov_1, and θcov was the fractional change of cov_2 from θ_T, respectively.

Statistical models

We attempted to add the inter-individual variability (η_i) into the parameters of each model, and it was assumed to be log-normally distributed. The expression for subject i is $P_i=P_{tv}$*exp(η_i), where P_i is the estimate for the model parameter of the i individual, P_{tv} is the typical population estimate, and η_i is the inter-individual random-effect assumed to have an expected mean 0 and variance ω_i^2.

The residual variability was modeled with an additive error model as shown: Y_{ij}=IPRE$_{ij}$+ε, where Y_{ij} and IPRE$_{ij}$ represent the jth observed or predicted blood pressure for the ith subject, respectively. ε is the residual random effect defined as being normally distributed with mean 0 and variance σ^2.

Software

The population analysis was performed with non-linear mixed effects modeling using NONMEM version 7.2 (Icon Development Solutions, Ellicott City, MD, USA). NONMEM runs were executed using Wings for NONMEM (WFN720, http://wfn.sourceforge.net). The first-order conditional estimation method with interaction (FOCE-I) was used throughout the analysis. Perl-speaks-NONMEM 3.5.3[16] was used to facilitate processing the NONMEM output and for parallel execution of the bootstrap. Xpose[17] was used to evaluate the goodness-of-fit of the models and for plotting.

Model evaluation

Graphical and non-parametric statistical methods were used for model evaluation. Goodness-of-fit plots, including plots of observed versus population and versus individual predicted values, individual weighted residuals (IWRES) versus individual predicted values and weighted residuals (WRES) versus time, were used to evaluate model bias. The final model was evaluated using a nonparametric bootstrap re-sampling technique. A total of 1000 bootstrap replicate datasets were generated by sampling randomly from the original data of study 1 with replacement. The accuracy of the model parameters was evaluated by comparing the 90% confidence interval of the parameter estimates from the bootstrap datasets with the parameter values obtained from the original dataset.

The predictive performance of the final model was validated internally using the data from study 1. A visual predictive check (VPC) based on 1000 simulations for the final model was used to evaluate the model. The measured time points were binned into one-hour intervals. For each bin, the median blood pressure and the 2.5th and 97.5th percentiles were calculated from the simulated data. The observed blood pressure and confidence interval of the simulated data were plotted together for visual inspection.

The data from study 1 were used as the developmental dataset for model building. After model evaluation and validation, the same structural model was used for the data from the remaining 3 studies. The ability of the final model to describe the observed data was also investigated using the visual predictive check. For generalization to future studies, the data from all 4 studies were also combined and analyzed using the structural model built in study 1. The same model-developing procedure introduced previously was also applied for the pooled data.

Results

The following equation containing two cosine functions was selected as the circadian rhythm model to describe the blood pressure changes over time:

$$BP_k(t)=Base_k+A_{1k}\cdot\cos[\frac{2\cdot\pi\cdot(t-PHS_1)}{0.5}]+A_{2k}\cdot\cos[\frac{\pi\cdot(t-PHS_2)}{0.5}]$$

In this equation, k=1 is systolic blood pressure, k=2 is diastolic blood pressure, $BP_k(t)$ is the blood pressure as a function of t (the unit of t is day), $Base_k$ is the rhythm-adjusted 24-h mean, A_{1k} and A_{2k} are the amplitude of the cosine terms, and PHS_1 and PHS_2 are the parameters for phase shifts of the cosine terms.

As shown in the plots of systolic and diastolic blood pressure versus time, the time trends of both blood pressure measurements were similar. The circadian rhythm models were developed successfully for diastolic and systolic blood pressure measurements, respectively (Figure 1). Because the phase-shift parameters in the two models were very close, the same phase-shift parameters were used for the final model in which systolic and diastolic blood pressure were modeled together. The parameter estimates and their corresponding standard error (in percentage points) obtained from the final model are listed in Table 2. The typical values of the rhythm-

Table 2. Model parameter estimates of the diastolic and systolic 24-h ABPM with 1000 nonparametric bootstrap procedures of Study 1.

Parameter	Annotations	Estimate (SEM%)	Shrinkage% (*P* value)	Bootstrap median	Bootstrap 95% CI
Cyclic fluctuations model parameters					
$Base_1$	Rhythm-adjusted 24-h mean SBP (mmHg)	140 (1.8)		140	136–145
$Base_2$	Rhythm-adjusted 24-h mean DBP (mmHg)	89.5 (1.8)		89.6	86.7–92.6
A_{11}	Amplitude first cosine term of SBP	7.52 (8.7)		7.52	6.37–8.79
A_{21}	Amplitude second cosine term of SBP	8.64 (9.1)		8.58	6.89–10.19
A_{12}	Amplitude first cosine term of DBP	5.61 (7.6)		5.60	4.70–6.50
A_{22}	Amplitude second cosine term of DBP	6.27 (9.3)		6.32	5.21–7.50
PHS_1	Phase-shift first cosine term	-0.652 (1.3)		-0.651	-0.668–0.862
PHS_2	Phase-shift second cosine term	3.61 (0.8)		3.61	3.50–3.69
Inter-individual variability					
ω_{Base1} (CV%)	Interindividual variability of $Base_1$	0.079 (20.6)	-0.68 (0.999)	0.079	0.061–0.094
ω_{Base2} (CV%)	Interindividual variability of $Base_2$	0.12 (21.3)	-0.48 (0.999)	0.12	0.094–0.146
ω_{A11} (CV%)	Interindividual variability of A_{11}	5.63 (31.8)	20.5 (0.232)	5.47	3.42–7.14
ω_{A21} (CV%)	Interindividual variability of A_{21}	4.73 (33.0)	17.9 (0.282)	4.74	3.12–6.91
ω_{A12} (CV%)	Interindividual variability of A_{12}	6.58 (37.6)	21.6 (0.234)	6.39	3.20–8.70
ω_{A22} (CV%)	Interindividual variability of A_{22}	6.71 (35.6)	16.6 (0.421)	6.36	4.05–8.83
ω_{PHS1} (CV%)	Interindividual variability of PHS_1	10.9 (27.5)	4.96 (0.933)	10.05	7.0–13.3
ω_{PHS2} (CV%)	Interindividual variability of PHS_2	1.24 (37.6)	0.23 (0.988)	1.17	0.59–1.6
Residual variability					
σ_{SBP}	Intraindividual residual variability of SBP (mmHg)	12.85 (6.5)	2.93	12.9	12.1–13.7
σ_{DBP}	Intraindividual residual variability of DBP (mmHg)	9.11 (7.9)	2.96	9.10	8.46–9.79

SEM%, standard error %; 95% CI, 95% confidence interval; CV%, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24-h ABPM, 24-h ambulatory blood pressure monitoring.

adjusted 24-h mean diastolic and systolic blood pressures were 140 mmHg and 89.5 mmHg, respectively. The standard error percentages of all fixed-effect parameters were less than 10%, indicating that these parameters were sufficiently accurate and that the blood pressures were well described by the final model. The goodness-of-fit plots (Figure 1) of the predicted and observed data indicated that the model adequately described the systolic and diastolic blood pressures over the entire 24-h period. The weighted residuals were evenly distributed around zero, and most of these were within an SD of ±2 of the normalized units. Individual plots (Figure 2) of observations, individual predictions and population predictions versus time also indicated the model's adequate capture of both systolic and diastolic blood pressure measurements. The covariates, including gender, age, weight and BMI, did not significantly increase the goodness of fit.

Of the 1000 bootstrap re-sampling datasets, 974 were minimized successfully with the covariance step. Table 2 presents the results of the bootstrap distributions for the parameters of each model. The medians of the bootstrap re-samples of all parameters were similar to the estimations based on the original dataset. In addition, the relatively small bootstrapped confidence interval of all parameters indicated the accuracy and precision of the final model.

A total of 1000 simulated datasets based on the model parameters and graphical forecasts were also evaluated. As shown in the visual predictive checks (Figure 3, Study 1) based on the estimations of the final model, the model prediction and the observed measurements of the systolic and diastolic blood pressures were in good agreement. This also implied that the final model satisfyingly captured the tendency of the 24-h blood pressure fluctuations.

For the 24-h blood pressure measurements in Studies 2, 3 and 4, the predictions of the same structural model were good. All parameter estimates were similar among the 4 studies (Table 3). The visual predictive check of these studies (Figure 3, Studies 2, 3, and 4) also illustrated that the circadian rhythm model could adequately describe 24-h blood pressure.

When the data of the 24-h blood pressure measurements were pooled from all 4 studies, the fluctuation model also performed well, and only slight differences were shown in the parameters between the pooled analysis and the 4 study analyses. This indicated that the developed circadian rhythm model was robust and predictable. The inter-individual variability versus study plot and the residual variability versus study plot implied that there were no remarkable differences in the parameters among studies. OFVs were not decreased significantly when inter-study variabilities were introduced into the model. No covariate was introduced as a significant factor into the pooled model.

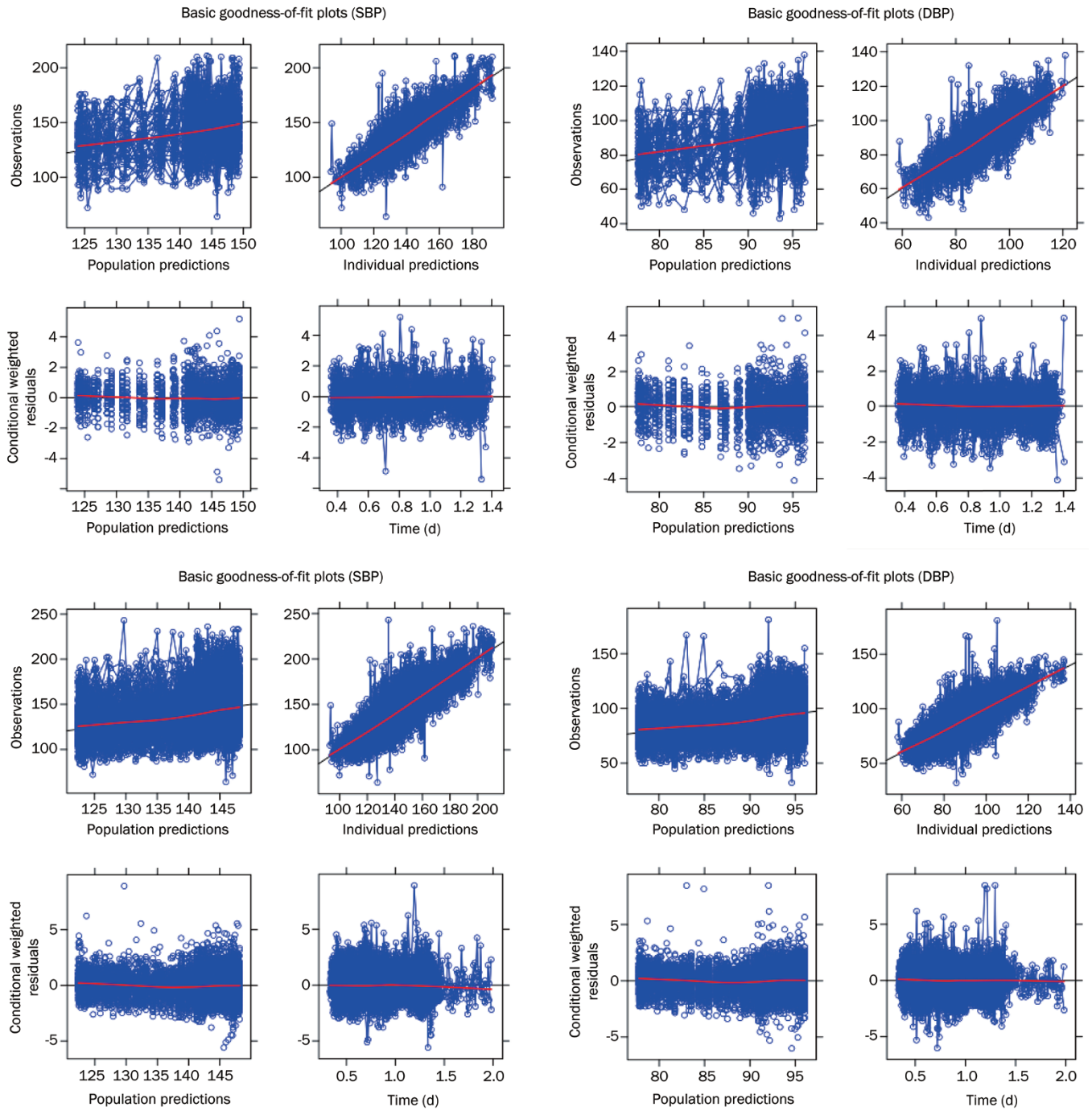

Figure 1. Basic goodness-of-fit plot of the final cyclic fluctuations model for systolic (left) and diastolic (right) 24-h ABPM in Study 1 (top) and pooled analysis (bottom).

Discussion

Compared to casual blood pressure measurements, more data points are measured by 24-h ABPM. Thus, 24-h ABPM provides a more precise diagnosis and better prediction of clinical outcomes in patients with hypertension and cardiovascular diseases. However, the indices of conventional analyses of 24-h ABPM, such as the trough-to-peak ratio, smoothness index, average 24-h BP and average daytime and nighttime BP, do not take full advantage of the features of large amounts of data. Population modeling methods can effectively use all measurements from 24-h ABPM and reduce the influence of different measurement schedules among subjects.

The circadian rhythm model was successfully applied in this study to capture the cyclic fluctuations of both systolic and diastolic blood pressures within 24 h. The rhythm-adjusted 24-h mean values of SBP and DBP from the model were almost

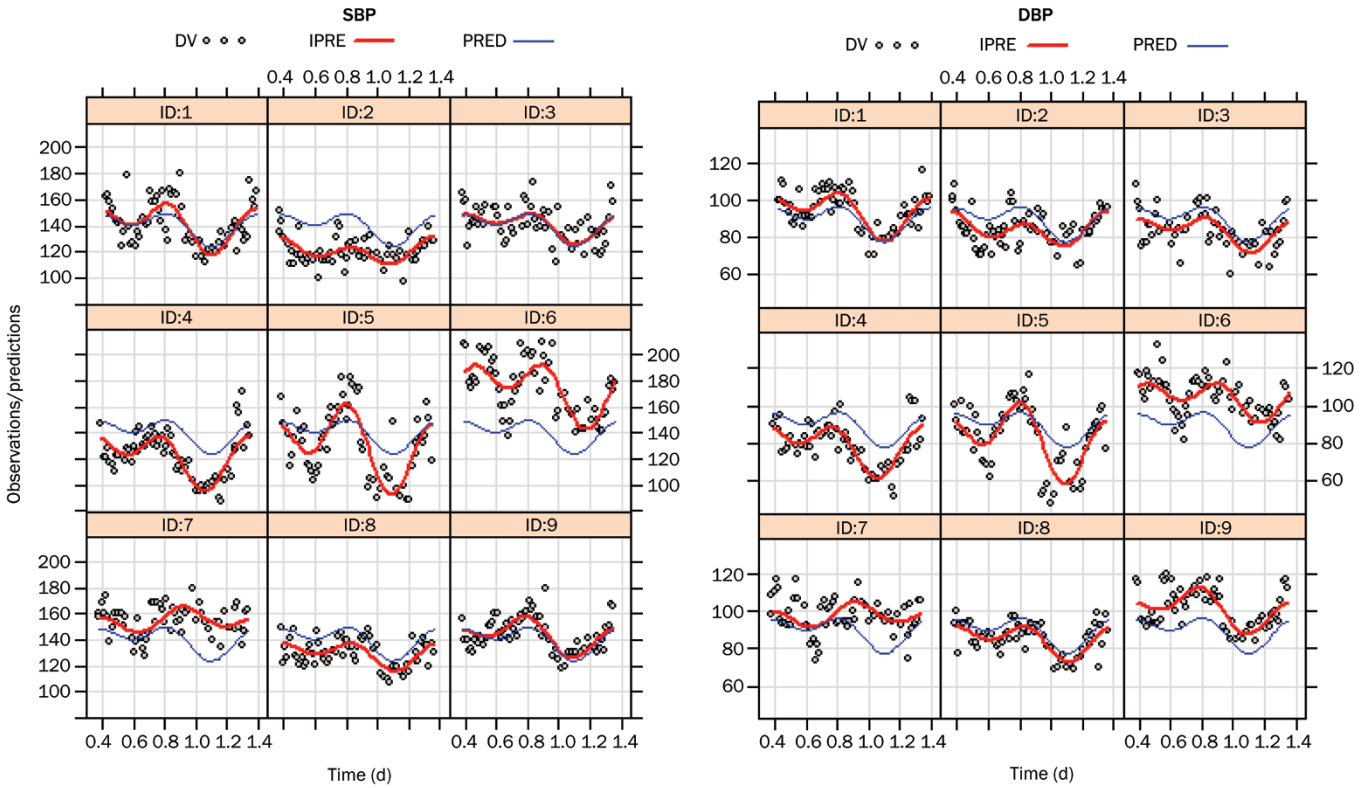

Figure 2. Individual model prediction of systolic (left) and diastolic (right) 24-h ABPM. Only the plots of the first 9 subjects were shown.

Table 3. Cyclic fluctuations model parameter estimates of the diastolic and systolic 24-h ABPM in Study 2, 3, and 4.

Parameter	Study 2 Estimate (SEM%)	Study 3 Estimate (SEM%)	Study 4 Estimate (SEM%)	Overall* Estimate (SEM%)
Cyclic fluctuations model parameters				
$Base_1$	144 (1.7)	138 (1.2)	136 (1.0)	139 (0.7)
$Base_2$	91.7 (1.8)	88.8 (1.2)	88.5 (0.8)	89.5 (0.7)
A_{11}	7.83 (8.5)	6.07 (8.6)	7.11 (9.2)	7.2 (4.6)
A_{21}	9.76 (8.2)	7.59 (7.6)	10.8 (6.3)	9.45 (4.7)
A_{12}	5.78 (5.5)	4.41 (6.1)	5.08 (8.5)	5.22 (4.8)
A_{22}	6.39 (10.1)	6.05 (9.8)	7.16 (7.0)	6.55 (5.1)
PHS_1	-2.18 (0.6)	-2.16 (0.3)	0.84 (1.1)	-2.16 (0.2)
PHS_2	3.61 (0.7)	3.58 (0.4)	4.58 (0.4)	3.59 (0.3)
Inter-individual variability				
ω_{Base1}	0.108 (26.2)	0.068 (23)	0.0728 (16.6)	0.0933 (13.4)
ω_{Base2}	0.112 (20.8)	0.075 (21.8)	0.0587 (22.7)	0.0899 (13.0)
ω_{A11}	0.422 (30)	0.515 (29.8)	0.494 (25.4)	0.457 (14.7)
ω_{A21}	0.492 (24.3)	0.825 (22.8)	0.420 (20.3)	0.519 (13.0)
ω_{A12}	0.327 (34.5)	0.523 (29.7)	0.506 (24.9)	0.439 (16.2)
ω_{A22}	0.547 (33)	0.660 (22.7)	0.415 (22.0)	0.502 (14.3)
ω_{PHS1}	0.0379 (25.6)	0.0128 (28.1)	0.0816 (23.3)	0.0296 (15.5)
ω_{PHS2}	0.0424 (29.5)	0.0182 (52.6)	0.0318 (31.7)	0.0390 (19.7)
Random variability				
σ_{SBP}	12.8 (6.7)	12.6 (6.9)	11.3 (5.9)	12.2 (3.4)
σ_{DBP}	9.28 (6.3)	9.74 (10)	8.96 (5.6)	9.23 (3.7)

SEM%, standard error %; *Combined data of Study 2, 3, and 4.

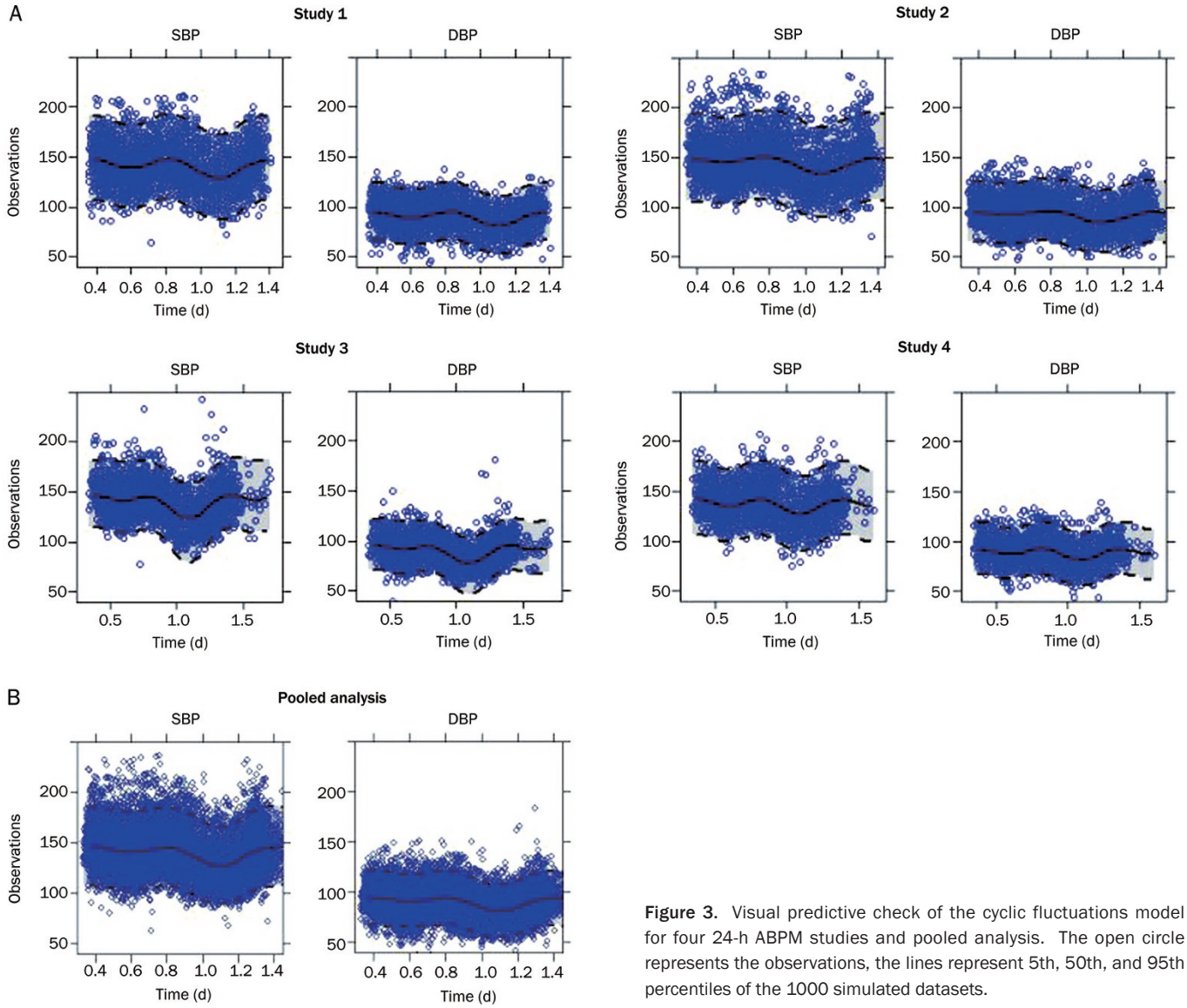

Figure 3. Visual predictive check of the cyclic fluctuations model for four 24-h ABPM studies and pooled analysis. The open circle represents the observations, the lines represent 5th, 50th, and 95th percentiles of the 1000 simulated datasets.

equivalent to the averaged values of those from the raw data. Compared with the published models for 24-h ABPM, which were studied in Europe[9, 10], rhythm-adjusted 24-h mean BPs (including SBP and DBP) were very close to those in Reference[10] but were slightly less than in that in Reference[9]. The likely reason is that only patients with mild-to-moderate hypertension were enrolled in our studies and in Reference[10], and no such criteria were mentioned in Reference[9]. In addition, the additive residual variabilities for both SBP and DBP were similar to those of previous models. However, there were some features of the circadian rhythm model in this study. First, the model structure changed from multiplication to addition based on goodness of fit. Second, the same phase-shift parameters were applied to describe both systolic and diastolic blood pressures in the model. Because the model development procedure was based on previous experience, these modifications most likely indicate that the cyclic pattern of blood pressure fluctuations in Chinese patients is slightly different from that in non-Chinese patients.

The predictive performance of the model was assessed in two steps. The first step was performed using a visual predictive check to evaluate the ability of the model to generate the data on which the model was built (Study 1). The second step involved 3 datasets from three other 24-h ABPM studies (Studies 2–4). In both steps, the model performed well and showed the ability to predict the central tendency of blood pressure in patients with mild to moderate hypertension in China with reasonable confidence. Furthermore, the fluctuating changes of blood pressure showed a "two peaks and a valley" feature in the visual predictive check plots. The "dipping pattern," which indicated that the average difference between daytime and nighttime systolic and diastolic BPs was 10%–20%, was also observed as an overall trend of all the studies. Although "non-dipper" changes (nocturnal decline of <10%) were found

in some patients (IDs 2 and 7 in Figure 2), the model's predictive performance in these subjects was good as well. This pattern in the patients is also an important source of inter-individual variability of the model parameters. Eating, physical activity and emotional state, which will affect blood pressure readings, were not recorded in these 4 studies and were therefore not included in the model. These influential factors should be collected in future 24-h ABPM studies and introduced into the model in an appropriate way to improve the accuracy of model predictions.

According to the regular circadian rhythm pattern of blood pressure fluctuations, individualized therapy based on the principle of time therapeutics has gradually received much more attention in the treatment of essential hypertension[18]. The cyclic fluctuation model developed in this study can be applied to estimate the variation in individual hypertensive patients. It also can provide the basis for individualized treatment, such as selecting the appropriate antihypertensive drugs and adjusting the dose and the time that medicine is taken.

In this study, the cyclic fluctuation model, which was built based on the data from study 1, was still able to achieve successful performance in fitting and predicting data from the other three studies. The general parameters were also obtained from the pooled data of four studies. The criteria for screening patients with mild-to-moderate hypertension in our studies also suggest the possibility of using this model for other antihypertensive studies. Moreover, the model parameters of all studies were very similar, indicating that this model has good productivity and extensive suitability and could be used as a reference in future 24-h ABPM studies. Blood pressure can be described and simulated at any time point using the developed model. In new antihypertensive drug development, the pharmacokinetic-pharmacodynamic model can be added to the circadian rhythm model to describe and predict blood pressures over time after drug administration. Using these models, different dosing regimens and study designs of new antihypertensive clinical trials can be simulated and assessed[19]. As a result, the uncertainty of new antihypertensive drug development could be reduced by answering a series of "what-if" problems based on these models.

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Author contribution

Yu-cheng SHENG designed the research and wrote the paper; Qing-shan ZHENG revised the paper; Yu-cheng SHENG, Juan YANG, and Ying-chun HE analyzed the data and plotted the figures; Kun WANG and Ling XU provided technical assistance.

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