# Trended Cosinor Change Model for Analyzing Hemodynamic Rhythm Patterns in Hemodialysis Patients

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***Abstract***—To describe circadian blood pressure (BP) patterns and linear interdialytic changes, a model was developed to describe simultaneously both the straight line change and oscillatory variation in BP and heart rate over an interdialytic interval in hemodialysis patients. Using this trended cosinor model, we simultaneously compared the impact of mean level of BP, linear changes over the interdialytic interval, and oscillatory changes in BP and its relationship with antihypertensive drug use. Neither a straight-line change model nor the cosinor model adequately described the BP variability in 12 750 BP measurements from 136 chronic stable hemodialysis patients. A combination of the 2 models that allowed for the oscillatory rhythmic pattern in BP variation to have an upward trend in the interdialytic period most accurately described the data. Time elapsed since the end of dialysis demonstrated a better model fit compared with the less meaningful clock time. More antihypertensive medication use was associated with increasing mean systolic, diastolic, and pulse pressure. Although the rate of change was blunted with increasing antihypertensive drug use, the impact on oscillatory change was U-shaped for systolic BP, direct for diastolic BP, and inverse for pulse pressure. A trended cosinor model better describes the change in BP in the interdialytic interval in hemodialysis patients, especially when time elapsed is measured from the end of dialysis. Antihypertensive drugs, though associated with higher average BP, are associated with blunted rate of change in BP over time. (***Hypertension*****. 2007;50:143-150.)**

**Key Words:** hemodialysis ■ hypertension ■ ambulatory blood pressure monitoring ■ circadian rhythms ■ statistical modeling

Hypertension is the single greatest cause of mortality in the world.[1] The diagnosis and management of hypertension is most commonly based on blood pressure (BP) recordings made in the physician offices. Better methods of assessment of BP are available, such as self-recorded measurements[2,3] or automatic ambulatory BP recordings.[4–7] Systemic arterial pressure demonstrates a distinct arterial rhythm that is related to the sleep–awake cycle, and ambulatory BP recordings can reveal such variations. Ambulatory BP monitoring in patients with chronic kidney disease has led to the identification of loss of nocturnal decline in BP,[8,9] which is associated with poor estimated glomular filtration rate.[10] Interpreting ambulatory BP recording is typically performed by averaging a large number of BP measurements and calculating average BP during the day and during the night, but such a reductionist approach obscures the rhythmic changes in BP over a 24-hour period.[11–13] To study this blunting in circadian variation, modeling BP using cosinor rhythmometry has been proposed.[14] The amplitude, periodicity, and time to peak and trough can all be analyzed using this technique. The application of this model in patients with essential hypertension has yielded valuable insights.[15]

In the renoprival state, gain of volume over an interdialytic period leads to increase in BP. The traditional cosinor model requires midline estimating statistic of rhythm (MESOR), defined as the average value of the rhythmic function fitted to the data to be flat.[14] Gain in volume over an interdialytic interval may cause a steady increase in systemic arterial pressure between 2 dialysis treatments, and the above assumption of a flat MESOR may no longer be tenable. Thus, a more complex model that includes terms for cosinor, as well as a straight-line change, would be more appropriate to describe the data. A trended cosinor model that includes both parameters has not been developed but can be useful to evaluate the impact of interventions on not only the mean BP but also on the rate of change in BP between dialyses and the amplitude of these variations.

The purpose of this report is to describe the development of a trended cosinor model. We then examine the association of the impact of antihypertensive drug therapy with BP patterns in hemodialysis patients using this model.

## Methods

This is a cross-sectional study performed at 1 of the 4 dialysis units in Indianapolis affiliated with Indiana University.

### Subjects

Patients ≥18 years of age who had been on chronic hemodialysis for >3 months and were free of vascular, infectious, or bleeding

Received March 28, 2007; first decision April 16, 2007; revision accepted April 21, 2007.

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***Hypertension*** **is available at http://www.hypertensionaha.org** **DOI: 10.1161/HYPERTENSIONAHA.107.091579**

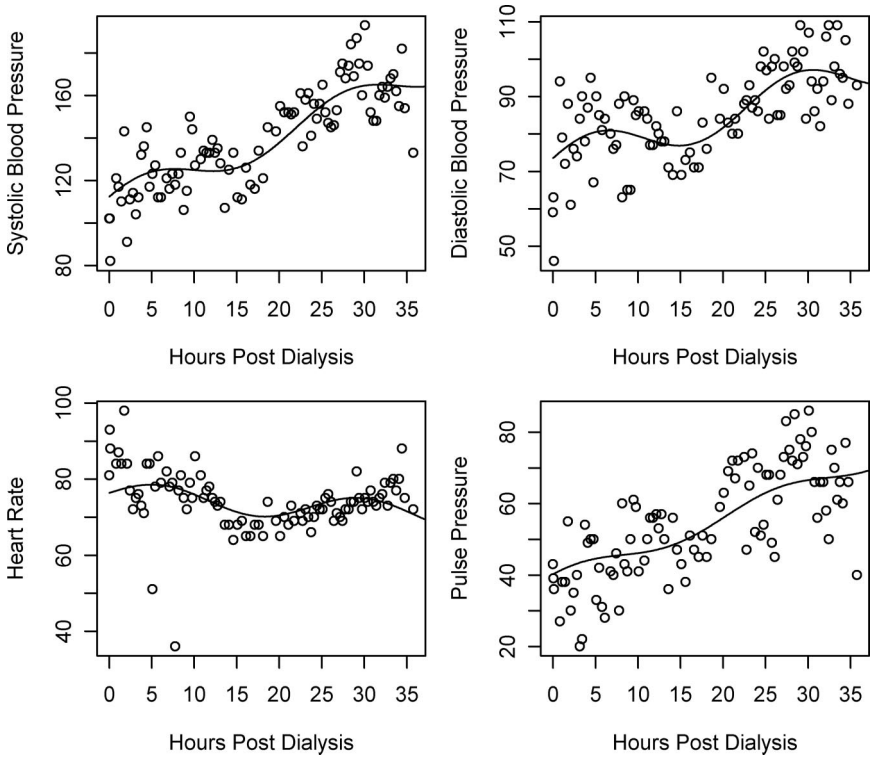


**Figure 1.** An example of observed BPs and heart rate and a fitted trended cosinor change model in an individual patient.

complication within 1 month were enrolled in the study. Those who missed ≥2 hemodialysis treatments over 1 month, used illicit drugs, and had chronic atrial fibrillation or body mass index of ≥40 kg/m$^2$ were excluded. Patients who had a change in dry weight or change in antihypertensive drugs within 2 weeks were also excluded. Presence or absence of hypertension was not a selection criterion. All of the patients underwent standard dialysis 3 times a week.

Anthropometric and demographic characteristics and antihypertensive medications actually taken by the patient were recorded. The study was approved by the institutional review board of Indiana University and the research and development committee of the Roudebush VA Medical Center, and all of the subjects gave written informed consent.

## Ambulatory BP Monitoring

Ambulatory BP monitoring was performed after the midweek hemodialysis session for 44 hours. Ambulatory BPs were recorded every 20 minutes during the day (6:00 AM to 10:00 PM) and every 30 minutes during the night (10:00 PM to 6:00 AM) using a Spacelab 90207 ABP monitor (SpaceLabs Medical Inc) in the nonaccess arm, as done previously.[13] Patients with <16 ambulatory BP recordings were excluded, because pattern recognition was not possible with a limited number of recordings. The remaining 136 patients had a combined 12 750 BP measurements. These data were exported to a relational database to allow for data management, as well as centering the time to that elapsed after dialysis using standard programming tools.

## Analysis

Original oscillometric data from each BP series were first synchronized for each individual by recomputing all of the times of sampling in hours from the end of dialysis to avoid differences among subjects dialyzing on different dialysis shifts. We used both clock time and resynchronized time postdialysis for model fit. We compared models that used time postdialysis with models that used clock time when modeling hemodynamic parameters over an interdialytic interval. In addition, we used a composite model where we used clock time for cosinor and time elapsed after dialysis for linear trends.

## Statistical Methods

To detect the presence of any diurnal pattern in hemodynamic measures in an interdialytic interval, we used the cosinor model.[14,15] This method entails fitting an oscillating curve to temporal hemodynamic variables, such as BP and heart rate, using some specified (eg, 24-hour) periodicity. The hemodynamic variables were obtained for ≈44 hours after hemodialysis. The cosinor model first considered to be describing the rhythmic cycle can be expressed as $y = b_0+b_1\times\mathrm{Cos}[(2\pi/24)t]+b_2\times\mathrm{Sin}[(2\pi/24)t]$ where $y$ represents the observed systolic BP, diastolic BP, pulse pressure or heart rate; $b_0$, $b_1$, and $b_2$ are regression coefficients; and $t$ represents time (eg, elapsed time after dialysis or clock time). The constant $2\pi/24$ represents the 24-hour periodicity of BP. The coefficient $b_0$ represents the 24-hour rhythm-adjusted mean BP also called the MESOR, defined as the average value of hemodynamic measure (BP, pulse pressure, or heart rate). The regression coefficients $b_1$ and $b_2$ are the coefficients for the cosine and sine component, respectively, and collectively describe the amplitude of the cosine curve, which is defined as amplitude$=\sqrt{b_1^2+b_2^2}$. The amplitude represents half of the extent of rhythmic change in a cycle approximated by the fitted curve, which implies that it can be interpreted as the mean deviation across the time span.

Although the cosinor model described is adequate for many biological processes that cycle over a 24-hour period, a fundamental issue not addressed with the cosinor model arises. This issue is that, over an interdialytic interval, not only are there oscillations in BP, there is also a systematic positive increasing trend because of the interdialytic volume expansion (see observed and modeled BP and heart rate, eg, in Figure 1). Thus, it was necessary to add an additional component to the cosinor model that allowed for the systematic change in BP in addition to the oscillation because of the BP cycle, which is modeled with the cosinor model. This generalized cosinor model, termed the trended cosinor model, is given as follows:

$$y=b_0+b_1\times Cos[(2\pi/24)t]+b_2\times Sin[(2\pi/24)t]+b_3\times t \quad (1)$$

which is the same as that given previously with the additional parameter accounting for any systematic linear change over time. Thus, the change model explicitly considers 2 types of change in a

unified manner: change that has a systematic linear component and change that oscillates.

In the trended cosinor model, the meaning of the amplitude is slightly modified to the extent of rhythmic change over and above the linear trend. The meaning of $b_0$ changes considerably from the MESOR in the standard cosinor model to the predicted value of BP−1 at $t=0$ (the −1 is necessary because cosine[0]=1). The mean BP is now conditional on the value of time in the generalized cosinor model because of the (assumed) non-0 slope.

When models were nested, comparisons of goodness of fit between models were made by testing the improvement in the log-likelihood ratio using a $\chi^2$ test. When models were not nested, comparisons of goodness of fit were make by comparing Akaike Information Criteria and the Bayesian Information Criteria. For Akaike Information Criteria and Bayesian Information Criteria comparisons, smaller numbers indicate a better model fit.

The mixed-effects models were fit in R using the nonlinear mixed-effects package (nlme).[16,17] Full information maximum likelihood was used for parameter estimation, and there was a random component associated with each fixed effect. The delta method with first-order Taylor expansion was used to estimate the SEs (and, thus, confidence limits and $P$ values) of functions of fixed effect parameters (eg, the amplitude).[18]

After development of a model where the parameters were unconditional, conditional models were developed where the number of BP medications (0, 1, 2, 3, 4, or more) was used to explain interindividual differences in change.

## Results

Between September 2003 and February 2005, we recruited 150 patients from 4 dialysis units staffed by the nephrology faculty of Indiana University. Adequate ambulatory BP record was obtained in 136 hemodialysis patients, and these were the subject of further analyses. The demographic and clinical characteristics of these patients are shown in Table 1.

Table 2 shows the sleep–awake BP and heart rate as a function of BP medications. Systolic BP fell 2.3 mm Hg and diastolic BP by twice as much; thus, the pulse pressure increased by 2.3 mm Hg. There was a strong direct relationship between antihypertensive drug use and systolic BP. The diurnal fall in BP was influenced by the number of antihypertensive drugs. Those who took a greater number of antihypertensive drugs had, in fact, a paradoxical increase in systolic and diastolic BP.

Table 3 shows the modeled linear and nonlinear effects for systolic BP. The average systolic ambulatory BP was 129.7 mm Hg (model 1). Just after dialysis, systolic BP was 124.4 mm Hg, and BP increased linearly at a rate of 0.26 mm Hg per hour elapsed postdialysis (model 2). The model fit was considerably improved with the linear term, as judged by the improvement in the log-likelihood function. Fitting the traditional cosinor model (model 3) improved the fit compared with model 1 (likelihood ratio improved) but deteriorated the fit compared with model 2 (higher Akaike Information Criteria and Bayesian Information Criteria). That is, the cosinor model was better than the no-slope model, but the model with a slope was better than the cosinor model. However, the straight-line model treats the oscillation about the line as error, but such oscillations may be important from a clinical perspective. The trended cosinor model discussed previously includes simultaneously oscillatory terms from the cosinor model and a slope from the straight-line change model. The trended cosinor model (model 4) was superior to any of the other models. Although sine and cosine coefficients were not significant, removal of either of these components deteriorated the model fit (data not shown). That is to say, although the mean of these coefficients did not differ significantly from 0, there was interindividual variation in these change coefficients that lead to a better fit when the model allowed the terms to be fit and to vary among the individuals. Thus, allowing for variation in systolic BP in a linear and oscillating fashion best described the data. Model 5 represents fitting the linear trend to time elapsed after dialysis and cosinor to clock time. Model fit was similar to

**TABLE 1. Clinical Characteristics of the Study Sample**

| Clinical Characteristic | Measurement |
|---|---|
| Age, y | 56±13 |
| Men, n (%) | 88 (65) |
| Race, n (%) | |
| White | 11 (8) |
| Black | 123 (90) |
| Other | 2 (2) |
| Predialysis weight, kg | 81.7±19.7 |
| Postdialysis weight, kg | 79.0±19.2 |
| BMI, kg/m$^2$ | 26.8±6.2 |
| Years of dialysis | 4±3 |
| Etiology of end-stage renal disease, n (%) | |
| Diabetes mellitus | 43 (32) |
| Hypertension | 76 (56) |
| Glomerulonephritis | 8 (6) |
| Obstruction | 1 (1) |
| Other | 8 (6) |
| Current smoker, n (%) | 50 (37) |
| Cardiovascular disease, n (%) | 67 (49) |
| Urea reduction ratio | 73±7.5 |
| Albumin, g/dL | 3.8±0.4 |
| Hemoglobin, g/dL | 12.5±1.5 |
| No. not receiving antihypertensive drugs, n (%) | 23 (17) |
| No. of antihypertensives in users, n (%) | |
| 1 | 33 (29) |
| 2 | 40 (35) |
| 3 | 17 (15) |
| >3 | 23 (21) |
| Nature of antihypertensive agent, n (%) | |
| Dihydropyridine calcium channel blockers | 46 (34) |
| Nondihydropyridine calcium channel blockers | 6 (4) |
| $\beta$-Blockers | 86 (63) |
| $\alpha$-Blockers | 7 (5) |
| Centrally acting agents | 25 (18) |
| Vasodilators | 19 (14) |
| Angiotensin-converting enzyme inhibitors | 53 (39) |
| Angiotensin receptor blockers | 21 (15) |
| Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers | 70 (51) |

± indicates SD.

**TABLE 2. Diurnal Blood Pressure Change Coefficients as a Function on BP Medications**

| Hemodynamic Parameter | Awake or Asleep | No. of BP Medications | | | | | Statistical Significance, *P* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Intercept | 1 | 2 | 3 | >3 | Sleep | Medication | Sleep×Medication |
| Systolic BP, mm Hg | Awake | 110.4* | 9 | 20.9* | 15.8† | 25.5* | 0.001 | <0.0001 | <0.0001 |
| | Sleep | −2.3‡ | −1.1 | −2.3‡ | 2.5‡ | 3.9‡ | | | |
| Diastolic BP, mm Hg | Awake | 68.3‡ | 0.2 | 7.5† | 1.9 | 10.1 | <0.0001 | 0.04 | <0.0001 |
| | Sleep | −4.6* | 0.7 | −0.3 | 1.7† | 2.7‡ | | | |
| Pulse pressure, mm Hg | Awake | 42.4* | 8.7† | 13.3* | 13.6‡ | 15.2‡ | <0.0001 | 0.002 | <0.0001 |
| | Sleep | 2.3* | −1.9‡ | −2.0‡ | 0.8 | 1.1 | | | |
| Heart rate, bpm | Awake | 89.5 | −5.7 | −6.2† | −13.3* | −9.3† | <0.0001 | 0.005 | 0.03 |
| | Sleep | −4.5* | 1.3† | 1† | 0.2 | 2.2* | | | |

*$P<0.001$; †$P<0.05$; ‡$P<0.01$.

model 4; therefore, we decided to use model 4 in all of the subsequent analyses.

To examine the impact of dialysis time on BP changes, we reanalyzed the data first by clock time starting at midnight and then centering the time such that the clock started at the end of dialysis for each patient. Table 4 shows that the model fit improved considerably for the straight-line model when time was counted from that elapsed after dialysis. In the case of the cosinor model, the clock time allowed for a slightly better model fit compared with the time elapsed after dialysis. (This inconsistency is why we fit model 5). The trended cosinor model had the best fit when time was counted after dialysis.

Circadian parameters for other BP components and heart rate are shown in Table 5. The amplitude of change in systolic BP was <1 mm Hg and was marginally statistically significant ($P=0.07$). On the other hand, increase in slope of 0.26 mm Hg/h was highly significant. For diastolic BP, the rate of change was approximately half that seen for systolic BP, and the amplitude of variation was twice as large as systolic BP. Pulse pressure increased at a rate that would lead to 6-mm Hg amplification over the 2-day interdialytic interval. No significant linear change was seen in heart rate. The peak-to-trough variation in amplitude in heart rate would average 5 mm Hg based on our data.

Figure 2 shows the representation of the modeled BP and heart rate. Undulations in systolic BP are gentle and nonsignificant, but a steady increase is notable. Diastolic BP has more notable undulations and a less steep trajectory compared with systolic BP. Heart rate has a flat trajectory and circadian variation that is most notable.

The impact of number of antihypertensive drugs on BP characteristics is shown in Table 6. Each medication increment was associated with an increase in the systolic BP of

**TABLE 3. Taxonomy of Models for Systolic Ambulatory BPs**

| | Model No. | | | | |
|---|---|---|---|---|---|
| Parameter | 1 Means Only | 2 Straight Line | 3 Cosinor | 4 Cosinor With Linear Term | 5 Cosinor With Linear Term* |
| Intercept | 129.7 (125.9 to 133.6)† | 124.4 (120.5 to 128.4)† | 129.8 (126 to 133.6)† | 124.4 (120.1 to 128.3)† | 124.3 (120.2 to 128.4)† |
| Slope | | 0.26 (0.18 0.33)† | | 0.26 (0.19 to 0.34)† | 0.26 (0.19 to 0.34)† |
| Sine coefficient | | | −1.2 (−2.3 to −0.07)‡ | −0.01 (−1.2 to 1.1) | −0.17 (−1.36 to 1.03) |
| Cosine coefficient | | | 0.004 (−1.08 to 1.09) | 0.97 (−0.09 to 2.03) to $P=0.072$ | −1.22 (−2.2 to −0.24)‡ |
| $\sigma$ | 15.348 | 14.213 | 14.125 | 12.926 | 12.927 |
| Pseudo $R^2$ | | 0.142 | 0.153 | 0.291 | 0.291 |
| AIC | 106 549 | 104 955 | 105 061 | 103 219 | 103 211 |
| BIC | 106 571 | 105 000 | 105 136 | 103 331 | 103 323 |
| LL | −53 271 | −52 472 | −52 521 | −51 595 | −51 590 |
| Model comparison | | 2 vs 1 | 3 vs 1 | 4 vs 1 | |
| | | $P<0.0001$ | $P<0.0001$ | $P<0.0001$ | |
| | | | 3 vs 2 | 4 vs 2 | |
| | | | $P<0.0001$ | $P<0.0001$ | |
| | | | | 4 vs 3 | |
| | | | | $P<0.0001$ | |

*Cosinor fitted to clock time and linear term to postdialysis time.
†$P<0.001$; ‡$P<0.05$.

**TABLE 4. Comparison of Clock Time Versus Time Elapsed Postdialysis on Model Fit for Systolic BP**

| Model | Time | AIC | BIC |
|---|---|---|---|
| Mean only | Clock time | 106 549 | 106 571 |
| | Time postdialysis | 106 549 | 106 571 |
| Straight line model | Clock time | 105 979 | 106 023 |
| | Time postdialysis | 104 955 | 105 000 |
| Cosinor model | Clock time | 105 053 | 105 127 |
| | Time postdialysis | 105 061 | 105 136 |
| Straight line+cosinor model | Clock time | 105 427 | 105 502 |
| | Time postdialysis | 103 219 | 103 331 |

AIC indicates Akaike Information Criteria; BIC, Bayesian Information Criteria. Smaller values represent better model fit.

6.3 mm Hg and diastolic BP of 2.7 mm Hg. Significant blunting in the rate of change of systolic and diastolic BP was seen with antihypertensive medication intake. No such blunting in pulse pressure was seen with medications. The amplitude of variation in systolic BP followed a U-shaped curve for systolic BP, reduction for diastolic BP, and increase for pulse pressure (Figure 3). The lower limit of 95% CI for patients on 2 or 3 antihypertensive medications cross 0 in the case of systolic BP. Therefore, these variations were not significant. There were significant differences between mean amplitudes for each parameter (systolic pulse pressure, diastolic pulse pressure, or heart rate) for the number of antihypertensive drugs.

Figure 4 shows the modeled curves of circadian systolic and diastolic BP by intake of antihypertensive agents. The linear slope in systolic BP is more than twice that of diastolic BP. Furthermore, the linear slope of change becomes flatter with increasing antihypertensive medication intake. The U-shaped nature in variation in amplitude is evident for systolic BPs, and blunting in variation in diastolic BP with increasing number of medications is seen.

## Discussion

This article describes the development of a trended cosinor model that includes both a straight line and cosinor to fit ambulatory BP data to hemodialysis patients. Counting time as hours elapsed from the end of dialysis provides a better model fit compared with the clock time. The trended cosinor model (model 4; Table 2) is superior to the straight-line model (model 2) or the cosinor model (model 3). Thus, it represents a conceptual advance over the existing cosinor model that has been used previously.[15]

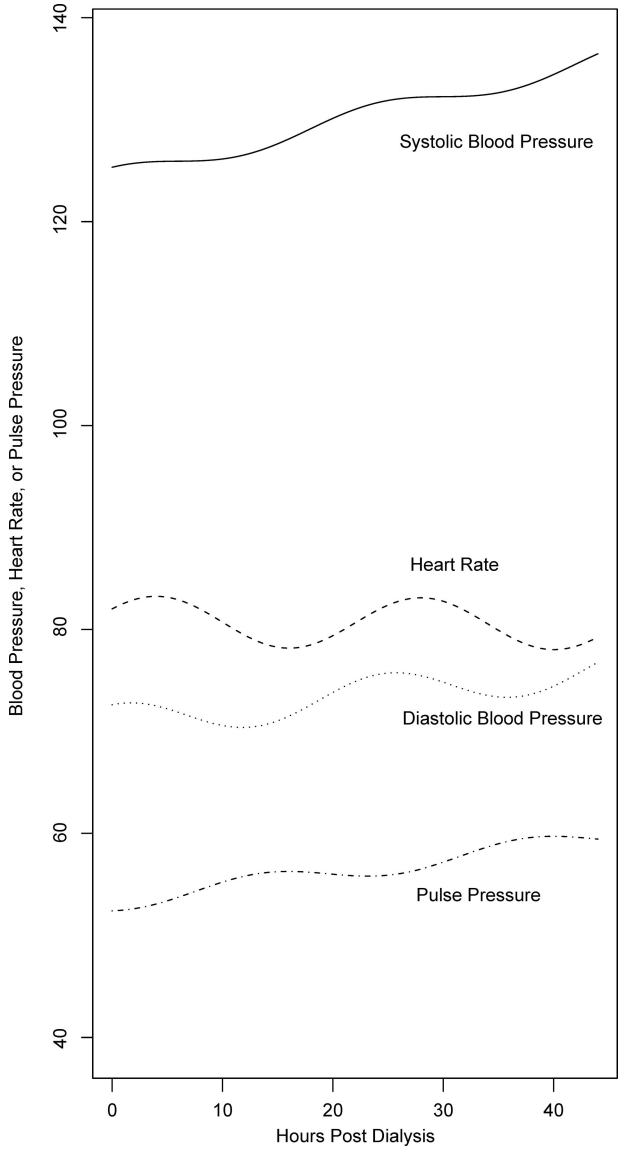


**Figure 2.** Modeled trended cosinor hemodynamic parameters in hemodialysis patients. Notice the linear trend in systolic, diastolic, and pulse pressure but lack thereof in heart rate. The amplitude of variation in systolic BP was <1 mm Hg and was of marginal statistical significance ($P=0.07$).

The clinical significance of the trended cosinor model is illustrated by comparing BP and heart rate data in 136 hemodialysis patients. For example, heart rate showed no straight-line trend and demonstrated substantial amplitude, but systolic BP had a significant straight-line trend and little

**TABLE 5. Combined Linear and Cosinor Model Parameters for Ambulatory BPs**

| Model Parameter | Systolic BP | Diastolic BP | Pulse Pressure | Heart Rate |
|---|---|---|---|---|
| Intercept | 124.4 (120.1 to 128.3)* | 70.9 (68.4 to 73.5)* | 53.4 (80.8 to 56.0)* | 80.9 (78.7 to 83.1)* |
| Slope | 0.26 (0.19 to 0.34)* | 0.12 (0.08 to 0.17)* | 0.14 (0.1 to 0.18)* | −0.006 (−0.06 to 0.05) |
| Sine coefficient | −0.01 (−1.2 to 1.1) | 0.37 (−0.37 to 1.1) | −0.37 (−1 to 0.31) | 2.2 (1.6 to 2.7)* |
| Cosine coefficient | 0.97 (−0.09 to 2.03), $P=0.072$ | 1.8 (1.2 to 2.5)* | −0.85 (−1.45 to −0.23)† | 1.3 (0.50 to 2)† |
| Amplitude | 0.97 (−0.08 to 2.03), $P=0.071$ | 1.9 (1.2 to 2.6)* | 0.92 (0.27 to 1.6)† | 2.5 (1.8 to 3.2)* |

Values represent means and 95% CIs.
*$P<0.001$; †$P<0.01$.

**TABLE 6. Impact of BP Medications on Ambulatory BP Dynamics**

| Model Parameter | None | Change per Medication |
|---|---|---|
| Systolic BP | | |
| Intercept, mm Hg | 112.4 (105.7 to 119)* | 6.3 (3.4 to 9.3)* |
| Slope, mm Hg/h | 0.40 (0.27 to 0.54)* | −0.07 (−0.13 to −0.02)† |
| Sine coefficient | 2 (0.10 to 4)‡ | −1.1 (−2 to −0.24)‡ |
| Cosine coefficient | 1.8 (−0.08 to 3.61), $P$=0.06 | −0.42 (−1.2 to 0.4) |
| Diastolic BP | | |
| Intercept, mm Hg | 65.9 (61.5 to 702)* | 2.7 (0.79 to 4.6)† |
| Slope, mm Hg/h | 0.22 (0.14 to 0.31)* | −0.05 (−0.09 to −0.02)† |
| Sine coefficient | 1.7 (0.47 to 3)† | −0.73 (−1.3 to −0.17)‡ |
| Cosine coefficient | 2.5 (1.3 to 3.6)* | −0.34 (−0.83 to 0.16) |
| Pulse pressure | | |
| Intercept, mm Hg | 46.5 (42.2 to 50.9)* | 3.7 (1.8 to 5.6)* |
| Slope, mm Hg/h | 0.18 (0.12 to 0.25)* | 0.02 (−0.05 to 0.01) |
| Sine coefficient | 0.32 (−0.85 to 1.5) | −0.36 (−0.88 to 0.15) |
| Cosine coefficient | −0.68 (−1.7 to 0.38) | −0.09 (−0.55 to 0.37) |
| Heart rate | | |
| Intercept, mm Hg | 86 (82.3 to 89.7)* | −2.7 (−4.3 to 1.1)* |
| Slope, mm Hg/h | 0.009 (−0.08 to 0.10) | −0.008 (−0.05 to 0.03) |
| Sine coefficient | 2.7 (1.7 to 3.7)* | −0.26 (−0.70 to 0.17) |
| Cosine coefficient | 1.12 (−0.19 to 2.4), $P$=0.09 | 0.07 (−0.51 to 0.64) |

Values represent means and 95% CIs.
*$P$<0.001; †$P$<0.01; ‡$P$<0.05.

amplitude (Table 4 and Figure 1). In contrast, diastolic BP had straight-line trend that was less steep than systolic BP and amplitude that was twice that of systolic BP. Thus, hemodialysis impacts systolic BP, diastolic BP, and heart rate differently. It is possible that volume factors predominantly affect systolic BP, whereas vascular tone may impact diastolic BP, potentially explaining the findings of our study.

In addition, we could detect important differences related to the number of drugs used to treat hypertension. Although the recognition of greater average systolic and diastolic BP with more medications is well documented, the analysis of the impact of the number of drugs and BP trends has not previously been possible.[19] The increasing number of antihypertensive drugs blunted the rate of rise in systolic BP and diastolic BP in the interdialytic period. In other words, those who received greater numbers of antihypertensive medications experienced less interdialytic BP increase; this increment was seen more for systolic than diastolic BP. The

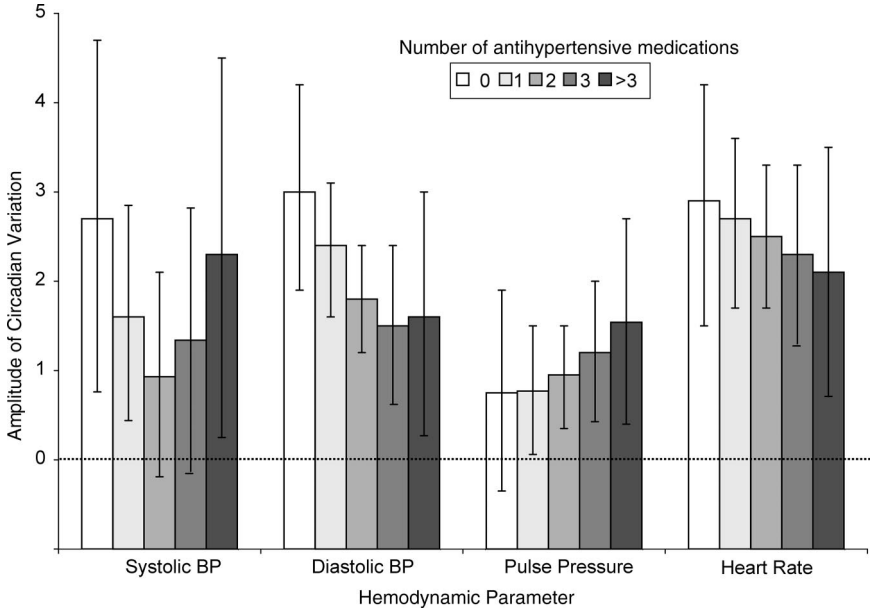


**Figure 3.** Amplitude of circadian variation as a function of the number of BP medications. Error bars are 95% CIs. When the lower limit of 95% CI crosses 0, the parameter is not statistically significant.

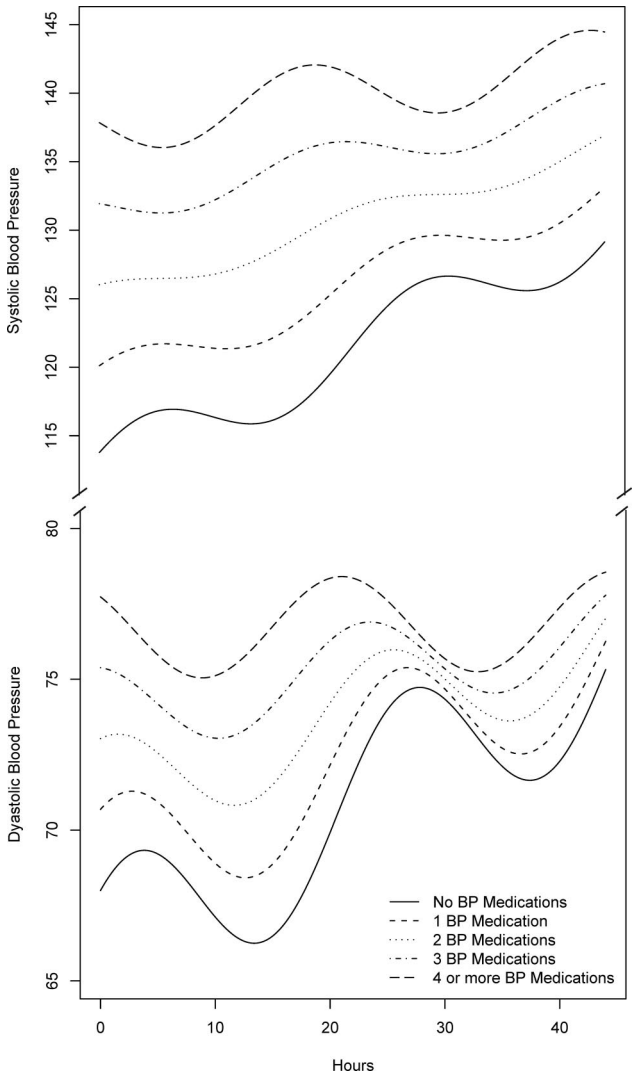


**Figure 4.** Modeled trended cosinor BP parameters as a function of the number of antihypertensive drugs. Increasing number of antihypertensive drugs blunted the linear trend in BP increase over an interdialytic interval.

amplitude of circadian changes in systolic BP was no different from 0 for those who received 2 or 3 drugs. In contrast, those who were on no drugs, 1 drug, or >3 drugs had non-0 amplitudes (Figure 2). For diastolic BP, reduction in amplitude was seen for increasing number of medications, such that pulse pressure amplitude increased with increasing number of medications. We were able to detect these patterns of changes as a direct result of the development of this statistical model.

Rodby et al[15] have previously described circadian rhythm in systolic and diastolic BP and heart rate in hemodialysis patients. In fact, the authors found that, despite interdialytic weight gain, there was no apparent increase in BP from day 1 to day 2 in dialysis patients. Fitting the cosinor model that assumes a flat MESOR may have obscured the linear trend in their data. Evidently, the cosinor model fit is reasonable when the linear trend is ignored in part because the misspecification recovers some of the linear change. Comparison of the amplitude of variation and linear changes in systolic BP using the trended cosinor model (model 4; Table 2 and Figure 1) demonstrates that the linear change is strong and overwhelms the relatively small variation in amplitude. Although population averaged circadian variation in diastolic BP and heart rate was detected, we found marginal circadian variation in systolic BP ($P=0.07$) despite a much larger study compared with Rodby et al.[15] This may be related to fitting fundamentally different models, as noted above, but may in part be related to the number of antihypertensive drugs. Hemodialysis patients using 0 to 1 antihypertensive drugs constituted 75% of the population reported by Rodby et al,[15] whereas these patients composed only 45% of our sample. Analysis of circadian variation in systolic BP was seen in patients taking 0 to 1 drugs but not in those taking 2 to 3 drugs. Thus, dampening of circadian variation in systolic BP seen in our sample could be related to patient and model differences.

Pulse pressure has emerged as 1 of the strongest predictors of total mortality in hemodialysis patients.[20,21] An increase in pulse pressure over the interdialytic interval was noted amounting to ≈6 mm Hg over 44 hours. This increase in pulse pressure may reach 10 mm Hg over the weekend. These data may explain, in part, why mortality is seen to be greatest just before the first dialysis of the week.[22] Increasing the number of antihypertensive drugs did not blunt the pulse pressure. Although these are observational data, the model developed can be used to study the impact of novel drugs or reduction in dry weight in randomized trials on pulse pressure and/or other hemodynamic measures.

## Perspectives

One practical application of this model could be to analyze patterns of BP changes with various antihypertensive drugs. Recent data in patients without chronic kidney disease demonstrate differences between β-blocker- and angiotensin-converting enzyme inhibitor–based therapies on central pressures, which were thought to be of prognostic importance.[23] Whether prognostic information can be derived from analysis of patterns of ambulatory BP changes obtained with the trended cosinor model remains to be seen. Drugs such as cyclosporine and erythropoietin often lead to an increase in BP in patients with chronic kidney disease.[24,25] Whether changes in amplitude or slopes predate the development of absolute increase in BP may shed light on the pathophysiology of these disorders. Future studies will analyze the impact of changes in these parameters in randomized, controlled trials of drugs, diets, and dry weight changes in hemodialysis patients. The development of the trended cosinor statistical model allows us to study the diagnostic and prognostic significance of the hemodynamic parameters in hemodialysis patients.

## Acknowledgments

We thank the staff of the dialysis units at Dialysis Clinics, Inc, Clarian Health, and the Roudebush VA Medical Center, as well as the faculty of the Division of Nephrology, who gratefully allowed us to the study their patients.

## Sources of Funding

This work was supported by the National Institutes of Health (National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases 5RO1 DK062030-04).

## Disclosures

None.

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