Disruption of Ultradian and Circadian Rhythms of Blood Pressure in Nondipper Hypertensive Patients

Santiago Perez-Lloret, Alejandro García Aguirre, Daniel P. Cardinali, Jorge E. Toblli

Abstract—Ultradian rhythms in blood pressure (BP) are known to exist, but their modification in hypertension is largely unknown. The present study was undertaken to assess the integrity of ultradian and 24-hour BP rhythms in dipper (n=100) and nondipper (n=20) hypertensive patients compared with 44 dipper normotensive individuals. Fourier analysis was used to fit ultradian (12, 8, and 6 hour) and 24-hour rhythms in BP and heart rate (HR). Mesor, amplitude, and acrophase were calculated for individual and overall rhythm curves. All subjects showed significant ultradian or 24-hour BP and HR rhythms. Systolic and diastolic BP mesor was higher in hypertensive patients compared with normotensive patients. The percentage of variability in ambulatory BP that could be explained by fitting ultradian and 24-hour rhythms was reduced in nondippers compared with normotensives or dippers. Amplitude of ultradian and 24-hour rhythms in BP increased in dippers and decreased in nondippers. Ultradian and 24-hour rhythms in HR did not differ among the 3 groups examined. Results indicate that in nondippers, blunted ultradian and 24-hour rhythm amplitude in BP was accompanied by a loss of rhythm integrity. (Hypertension. 2004;44:311-315.)

Key Words: blood pressure monitoring, ambulatory ■ human ■ hypertension, arterial ■ circadian rhythm

Circadian rhythm in blood pressure (BP) has been recognized as a prognosis marker in hypertensive patients.1 In normotensives as well as in noncomplicated hypertensive patients, a significant nocturnal decline in BP occurs, although in hypertensive patients, BP oscillates at a higher level. Nondipper hypertensive patients (ie, those in whom nighttime BP drop is <10%) have a worse prognosis as a result of increased target organ damage.2 In this group, significantly greater left ventricular hypertrophy, microalbuminuria, and stroke frequency have been described.2,3 Determination of ultradian components of BP rhythm (ie, those rhythmic components with a period <24 hours) has often been used as a tool to improve accuracy of the mathematical analysis of 24-hour rhythm parameters.4 However, because ultradian rhythms have been shown to vary independently of 24-hour rhythms in various situations,5,6 the possibility arises that their genesis and regulation could be somewhat independent from those regulating 24-hour rhythmicity.

We undertook the present study to compare ultradian rhythm parameters in normotensives and dippers and nondipper hypertensive patients. Because disturbances in 24-hour rhythms were implicated in the physiopathology of hypertension, we also assessed the integrity of 24-hour and ultradian rhythms in the same patient groups.

Materials and Methods

Patients

Among 265 patients who underwent ambulatory BP monitoring (ABPM), 180 were included in this study. To be included, each patient’s recording should extend for ≥22.5 hours but not >25.5 hours and with <5 single measurements missing. Patients were classified as hypertensive if they were under pharmacological treatment or if they showed an average diurnal BP of >135/85 mm Hg or a nighttime BP >120/75 mm Hg.7 One hundred thirty patients were classified as hypertensive and 50 as normotensive by using these criteria. Experimental protocol and the process for obtaining informed consent were approved by the hospital review and ethics committee.

Twenty-Four–Hour ABPM

Noninvasive ABPM was performed on a normal weekday by means of automatic monitor Accutrack II (Suntech Medical Instruments), validated by the standard criteria of the Association for the Advancement of Medical Instrumentation and the British Hypertension Society. Detailed features of the Accutrack II were described previously.8,9 The monitor was placed on the nondominant arm and set to take BP readings every 30 minutes during the whole 24-hour period.

Time Series Analysis

A fundamental rhythm of 24 hours with 3 harmonics of 12, 8, and 6 hours was fitted to the original time series recorded from each of the 180 patients by Fourier analysis.6,8,10 A 24-hour rhythm was considered to be present if the individual function within a 24-hour period could be fitted with a significance of P<0.05 by least-square analysis (variability ratio [VR]). Consecutively, residual differences
were tested in the same manner for the presence of significant ultradian rhythms (Figure 1). Rhythms were tested independently from each other and in strict order (eg, 12, 8, and 6 hours). For each rhythm of BP and heart rate (HR), mesor, amplitude, and acrophase were calculated (Figure 1). The overall curve was calculated by the addition of all 4 rhythms according to the formulas used previously.6 Significant overall rhythms could be found whenever the 24-hour rhythm or \( H_1 \) of the ultradian rhythms showed statistical significance. The difference between the peak and the trough value as well as the timing of the peak are given for overall rhythm (Figure 1).

VR is the fraction of the total variability that can be explained by each individual rhythm-fitted curve or by the overall rhythm-fitted curve.11 This parameter is obtained by least-square analysis and is homologous to the \( R \) regression coefficient. VR is independent from other rhythm parameters because it only measures the resemblance of the fitted and the original curves and not its shape. Lower VR values suggest that the sample is subjected to random variations that cannot be described adequately by fitting a rhythm, whereas VR high values mean that original curve variability is influenced mainly by a rhythm, regardless of its origin. Thus, VR value can be used as an indicator of rhythm integrity. Rhythm parameters were only analyzed in those subjects who showed significant rhythms as demonstrated by a VR \( P \) value <0.05 (least-squares analysis).

Cumulative Sums Derived Day-Night BP Differences
In addition to evaluation of 24-hour rhythm amplitude by Fourier method, diurnal and nocturnal BP means were calculated by cumulative sums analysis (cusum).12 When the difference between diurnal and nocturnal cusum of systolic BP (SBP; cusum-derived circadian alteration magnitude [CDCAM])12 was <10% of diurnal SBP, the patient was classified as nondipper.2 This method has been shown previously to be the most reproducible in classifying day-night BP differences, especially in aged groups13 and has been used extensively to study 24-hour rhythm disturbance in relation to hypertension.

Patients showing a reversed pattern of BP (ie, when BP rises at night instead of falling) were excluded from the sample. Reversed BP patterns can affect cusum analysis14 and were assessed by visual inspection of original recordings.

One hundred hypertensive patients were classified as dippers and 20 as nondippers. Ten subjects were excluded from the sample because of reversed BP patterns. Age, body mass index (BMI), or gender did not differ between the final sample and excluded patients. From the 50 normotensive subjects, 44 were dippers and 6 nondippers. For comparison with hypertensive groups, only the normotensive dipper group was used. No further analyses were performed with nondipper normotensive patients because of the small size of the sample.

Statistical Analysis
Data were analyzed using 1-way ANOVA followed by Bonferroni post hoc tests. Correlations were analyzed by Pearson coefficient. In both cases, analyses were also performed after adjustments for age and gender. Percentages were analyzed by \( \chi^2 \) test. Data are shown as mean \( \pm \) SEM. In all cases, \( \alpha \) was considered \( \leq 0.05 \).
Demographic data are summarized in Table 1. Hypertensive patients were on average significantly older than normotensives; dipper patients were more frequently males. In hypertensive patients, daily BP was higher than in normotensives, whereas in nondippers, nocturnal BP was higher than normotensives or dippers. Time elapsed from diagnosis was similar in dipper and nondipper patients, as shown in Table 1.

All subjects studied showed significant overall rhythms in BP and HR. Parameters of overall rhythms did not differ in dipper and nondipper patients, as shown in Table 1.

Age correlated with 12-hour rhythm amplitudes in DBP (r = 0.2; P = 0.04) and with 24-hour and 12-hour rhythm amplitudes in HR (r = -0.27; P = 0.001 and r = -0.20, P = 0.03, respectively) as well as with 12-hour and 8-hour rhythm amplitudes in DBP (r = 0.32, P = 0.003 and r = 0.29, P = 0.002, respectively). Age also influenced negatively VR coefficient of 24-hour rhythm in DBP, SBP, and HR (respectively, r = -0.20, P = 0.009; r = -0.19, P = 0.014; and r = -0.22, P = 0.003). VR coefficient of 8-hour rhythm in SBP correlated with age (r = 0.21; P = 0.006). Trough-peak difference in HR overall rhythm was also related to this parameter (r = -0.29; P = 0.0001).

Treated hypertensive patients showed significantly lower BP levels compared with untreated hypertensive (diurnal SBP P = 0.001; nocturnal SBP P = 0.01; diurnal DBP P = 0.003; nocturnal DBP P = 0.01; 1-way ANOVA). One-way ANOVA showed that pharmacological treatment affected time-to-peak (F = 3.1; P = 0.01) and VR (F = 2.6; P = 0.025) of overall HR rhythm.

In Figure 2, parameters of the SBP, DBP, and HR overall rhythm are depicted (Figure 2A, 2B, and 2C, respectively). In SBP, nondippers showed a reduction of VR coefficient with respect to both normotensives and dippers (P = 0.0001; ANOVA followed by Bonferroni test). The mesor was higher in dippers and nondippers than in normotensives (P = 0.0001; ANOVA followed by Bonferroni test). Trough-peak difference was higher in dippers compared with nondippers and lower in nondippers compared with both normotensives and dippers (P = 0.0001; ANOVA followed by Bonferroni test). Similar results were obtained for DBP except for the mesor, which was higher only in nondippers compared with normotensives and for trough-peak difference, which was similar in normotensive and dipper hypertensive patients.

No significant differences were apparent in time-to-peak for the 3 variables analyzed or in all other parameters for HR overall rhythm. Similar results were obtained after adjusting for gender and age (data not shown).

Parameters of individual rhythms were further analyzed and are shown in Table 2. Significant decrements in the amplitudes and VR coefficients of 24- and 12-hour SBP and DBP rhythms in nondippers were observed. Additionally, significantly fewer subjects in the nondipper groups showed 24-hour SBP and DBP rhythms.

### TABLE 1. Demographic Data of Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive (n = 44)</th>
<th>Dippers (n = 100)</th>
<th>Nondippers (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% of males)</td>
<td>44 (16)</td>
<td>100 (62)*</td>
<td>20 (35)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4 ± 0.5</td>
<td>27.0 ± 0.4</td>
<td>27.8 ± 1.2</td>
</tr>
<tr>
<td>Age</td>
<td>49.0 ± 1.8</td>
<td>55.7 ± 1.2†</td>
<td>59.1 ± 2.7†</td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>...</td>
<td>5.6 ± 0.3</td>
<td>6.0 ± 0.6</td>
</tr>
<tr>
<td>Antihypertensive treatment, %</td>
<td>...</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Angiotensin receptor antagonist</td>
<td>...</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>β blockers</td>
<td>...</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Ca channel antagonist</td>
<td>...</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Multiple drug</td>
<td>...</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Angiotensin converter enzyme inhibitor</td>
<td>...</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Other treatments (%)‡</td>
<td>10</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>

SBP

<table>
<thead>
<tr>
<th></th>
<th>Nocturnal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive (n = 44)</td>
<td>124.6 ± 1.0</td>
<td>139.6 ± 1.6†</td>
<td>134.5 ± 4†</td>
</tr>
<tr>
<td>Dippers (n = 100)</td>
<td>98.0 ± 1.0</td>
<td>106.0 ± 1.3†</td>
<td>119.3 ± 3.7†§</td>
</tr>
<tr>
<td>Nondippers (n = 20)</td>
<td>59.5 ± 1.0</td>
<td>62.1 ± 0.9</td>
<td>69.5 ± 2.9†</td>
</tr>
</tbody>
</table>

DBP

<table>
<thead>
<tr>
<th></th>
<th>Nocturnal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive (n = 44)</td>
<td>79.2 ± 0.8</td>
<td>86.0 ± 1.1</td>
<td>82.0 ± 2.8</td>
</tr>
<tr>
<td>Dippers (n = 100)</td>
<td>75.0 ± 0.8</td>
<td>84.0 ± 1.3†</td>
<td>87.0 ± 2.5</td>
</tr>
<tr>
<td>Nondippers (n = 20)</td>
<td>59.2 ± 1.0</td>
<td>62.1 ± 0.9</td>
<td>69.5 ± 2.9†</td>
</tr>
</tbody>
</table>

*P < 0.05 vs normotensives; χ² test.
†P < 0.05 vs normotensives; 1-way ANOVA test followed by Bonferroni post hoc test.
‡Benzodiazepine, alluprinol, and aspirin.
§P < 0.05 vs dipper hypertensive patients; 1-way ANOVA test followed by Bonferroni post hoc test.

**Results**

Demographic data are presented in Table 1. Hypertensive patients were on average significantly older than normotensives; dipper patients were more frequently males. In hypertensive patients, daily BP was higher than in normotensives, whereas in nondippers, nocturnal BP was higher than normotensives or dippers. Time elapsed from diagnosis was similar in dipper and nondipper patients, as shown in Table 1.

All subjects studied showed significant overall rhythms in BP and HR. Parameters of overall rhythms did not differ between genders. Amplitude of 24-hour rhythm in diastolic BP (DBP) was higher in males than females (9.8 ± 0.4 versus 7.9 ± 0.4 mm Hg, respectively; P = 0.002; ANOVA). VR coefficient of 24-hour rhythm in DBP and SBP was also higher in males (respectively, 0.62 ± 0.02 versus 0.52 ± 0.01 males versus females, P = 0.001; 0.62 ± 0.02 versus 0.53 ± 0.02, P = 0.002; ANOVA). There was no significant correlation between BMI and any rhythm parameter examined.

Age correlated with 12-hour rhythm amplitude in DBP (r = 0.2; P = 0.04) and with 24-hour and 12-hour rhythm amplitudes in HR (r = -0.27, P = 0.001 and r = -0.20, P = 0.03, respectively) as well as with 12-hour and 8-hour rhythm amplitudes in SBP (r = 0.32, P = 0.003 and r = 0.29, P = 0.002, respectively). Age also influenced negatively VR coefficient of 24-hour rhythm in DBP, SBP, and HR (respectively, r = -0.20, P = 0.009; r = -0.19, P = 0.014; and r = -0.22, P = 0.003). VR coefficient of 8-hour rhythm in SBP correlated with age (r = 0.21; P = 0.006). Trough-peak difference in HR overall rhythm was also related to this parameter (r = -0.29; P = 0.0001).
Systolic CDCAM correlated with the different rhythm parameters in the hypertensive group. In general, the results were similar to those obtained by comparing dipper and nondipper patients (data not shown). Additionally, there was correlation between systolic CDCAM and amplitude of 6-hour SBP and DBP rhythms ($r=0.43$, $P=0.0001$ and $r=0.38$, $P=0.007$, respectively). VR coefficient of 8-hour SBP rhythm also correlated with systolic CDCAM ($r=0.38$; $P=0.007$).

**Discussion**

The foregoing results indicate that in nondipper patients, reduction of 24-hour, 12-hour, and 8-hour SBP and DBP rhythm amplitudes was accompanied by alteration of the integrity of rhythms, as demonstrated either by abolition of the rhythms or by a lower VR coefficient (in those who did display significant rhythms). HR rhythms were similar in hypertensive and normotensive subjects. Age and gender influenced some parameters of the rhythms. Differences in composition regarding these variables of dipper and nondipper patient groups were not likely to be a significant bias of the study because statistical analysis adjusting for the effect of those variables yielded similar results to the original ones. Pharmacological treatment reduced BP levels significantly and affected HR rhythms but not BP rhythms.

Blunted day-night rhythm in autonomic 24-hour heart control of hypertensive patients has been demonstrated by spectral analysis of R-R interval. It has been suggested that a reduced nighttime drop of heart sympathetic tone in nondippers would lead to observed dampening in 24-hour BP rhythm amplitude. Indeed, inadequate stroke volume and cardiac index nighttime fall were found in nondipper patients. Our findings of lack of changes in HR rhythms are at odds with this. A possible explanation to interpret our results is that Fourier analysis of HR may not be sensitive enough for detecting such modifications.

Findings of a small group of normotensives showing nondipping patterns and that dipper and nondipper hypertensive patients did not differ in time from diagnosis may be an indication that rhythm disturbances are independent from hypertension but are aggravated during the course of the disease by unknown factors. Nondipping BP pattern is thought to worsen hypertension prognosis because of persistent BP load throughout the day. Because in certain experimental models circadian desynchronization decreases survival rates, the possibility should be considered that impaired adaptations to routine 24-hour or ultradian conditions could contribute to persistent BP load in addition to a worse prognosis in nondipper patients.

Determination of ultradian components of BP rhythm has often been used as a tool to improve accuracy of the mathematical analysis of 24-hour rhythm parameters, but it has been proposed recently that they could vary independently from 24-hour rhythms. Our results do not support such a conclusion but further indicate that independence does not occur as far as ultradian and 24-hour rhythms in nondippers. Moreover, our results show that in nondipper patients, reduction of 24-hour, 12-hour, and 8-hour SBP and DBP rhythm amplitudes was accompanied by an alteration in the integrity of rhythms. It will be of interest to assess whether alterations in ultradian rhythms bear prognostic implications as do those of 24-hour rhythm.

A possible explanation for the lack of independence of ultradian and 24-hour rhythms is that ultradian rhythms are just a mathematical artifact necessary to model the true shape of the 24-hour BP rhythm, which is not a perfect sine wave. Nonetheless, some speculations on the origin of ultradian...
rhythms can be entertained. For example, 8-hour oscillations occur in circulating endothelin-1 levels, and some studies demonstrated that 90-minute ultradian rhythms exist in cardiovascular parameters and in several hormones.

**Perspectives**

Because reduced 24-hour and ultradian BP rhythms integrity in addition to blunted 24-hour rhythm amplitude were observed in this study, the possibility should be considered that chronobiological alterations are at least in part responsible for nondipping BP profile. Because HR rhythm disturbances were not apparent, autonomic heart dysfunction as the cause of nondipper BP patterns is not supported by the present findings. Reduced amplitude of ultradian rhythms was also observed in nondipper patients, pointing out the need to extend rhythm research in hypertension to ultradian frequencies.

**References**


Disruption of Ultradian and Circadian Rhythms of Blood Pressure in Nondipper Hypertensive Patients
Santiago Perez-Lloret, Alejandro García Aguirre, Daniel P. Cardinali and Jorge E. Toblli

Hypertension. 2004;44:311-315; originally published online July 26, 2004;
doi: 10.1161/01.HYP.0000138856.39145.81
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/44/3/311

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/