**Chronotherapy in Resistant Hypertension**

**Chronotherapy Improves Blood Pressure Control and Reverts the Nondipper Pattern in Patients With Resistant Hypertension**

Ramón C. Hermida, Diana E. Ayala, José R. Fernández, Carlos Calvo

**Abstract**—Therapeutic strategies in resistant hypertension include adding another drug or changing drugs in search for a better synergic combination. Most patients, however, receive all of their drugs in a single morning dose. We have evaluated the impact on the circadian pattern of blood pressure on modifying the time of treatment without increasing the number of prescribed drugs. We studied 250 hypertensive patients who were receiving 3 antihypertensive drugs in a single morning dose. Patients were randomly assigned to 1 of 2 groups according to the modification in their treatment strategy: changing 1 of the drugs but keeping all 3 in the morning or the same approach but administering the new drug at bedtime. Blood pressure was measured for 48 hours before and after 12 weeks of treatment. There was no effect on ambulatory blood pressure when all of the drugs were taken on awakening. The baseline prevalence of nondipping (79%) was slightly increased after treatment (86%; P=0.131). The ambulatory blood pressure reduction was statistically significant (9.46/6.0 mm Hg for systolic/diastolic blood pressure; P<0.001) with 1 drug at bedtime. This reduction was larger in the nocturnal than in the diurnal mean of blood pressure. Thus, whereas only 16% of the patients in this group were dippers at baseline, 57% were dippers after therapy (P<0.001). Results indicate that, in resistant hypertension, time of treatment may be more important for blood pressure control and for the proper modeling of the circadian blood pressure pattern than just changing the drug combination. *(Hypertension. 2008;51:69-76.)*

**Key Words:** resistant hypertension ■ ambulatory blood pressure monitoring ■ circadian rhythm ■ chronotherapy ■ dipper ■ nondipper

Hypertension has been defined as resistant to treatment, or refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of ≥3 antihypertensive drugs in adequate doses has failed to lower systolic (SBP) and diastolic (DBP) blood pressure (BP) sufficiently.1,2 Patients with resistant hypertension are at a greater risk for stroke, renal insufficiency, and morbid cardiovascular events than patients for whom BP is well controlled by medical therapy.3 Accordingly, there is increasing interest on how to treat patients with resistant hypertension.

Therapeutic strategies in resistant hypertension currently include adding another drug or changing one drug for a different one in the search for a potentially better synergic combination.1,2 Most hypertensive patients, including those with resistant hypertension, however, receive all of their antihypertensive drugs in a single morning dose.4 Previous studies on the BP pattern of patients with resistant hypertension5,6 have not taken into consideration the potential influence in the results of the time of treatment. In fact, time of administration of antihypertensive drugs and its potential impact on the BP control of patients with apparent resistant hypertension have only been addressed occasionally.7,8

With the use of ambulatory BP monitoring (ABPM), Muxfeldt et al6 reported a 69% prevalence of nondipping (<10% decline in nocturnal mean relative to the diurnal mean of BP) in patients with resistant hypertension. Recent results indicate that nondipping is partly related to the absence of homogeneous 24-hour therapeutic coverage in patients treated with single morning doses.4 A recent cross-sectional study investigated the impact of treatment time on the BP pattern in 700 patients with resistant hypertension.8 Results indicated that the percentage of patients with controlled ambulatory BP was double in patients taking 1 drug at bedtime compared with those taking all of their medication on awakening. Moreover, the prevalence of nondipping was reduced from 82% to 57% when patients received 1 drug at bedtime.8 Accordingly, this prospective randomized trial evaluated the impact on the circadian pattern of BP and the degree of ambulatory BP control on modifying the time of treatment without increasing the number of prescribed drugs in patients with resistant hypertension.
Methods
An expanded Methods section can be found in the data supplement online at http://hyper.ahajournals.org.

Subjects
This prospective trial was conducted at the Hospital Clínico Universitario, Santiago de Compostela, between January 2003 and June 2005. Shift workers, heavy drinkers (alcohol intake >80 g/d), heavy smokers (>20 cigarettes per day d), and heavy exercisers were excluded, as were individuals with type 1 diabetes or secondary arterial hypertension and cardiovascular disorders, including concomitant unstable angina pectoris, heart failure, stroke, life threatening arrhythmia, nephropathy, and retinopathy, previous (within the last year) myocardial infarction, or coronary revascularization as revealed by thorough clinical evaluation according to the standardized protocol at the hypertension unit of the hospital. Inclusion criteria required a diagnosis of uncontrolled hypertension, first based on conventional BP measurements (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg). Patients were also required to have uncontrolled hypertension based on ABPM, ie, either the diurnal (awake) mean >135/85 mm Hg for SBP/DBP or the nocturnal (sleep time) mean >120/70 mm Hg. Moreover, inclusion criteria required that patients were treated for ≥3 months with a stable scheme consisting of 3 antihypertensive drugs in a single morning dose, with an adequate combination and dose. For this trial we screened 312 patients and identified 265 who met these inclusion/exclusion criteria. Among these, 250 (136 men and 114 women), 60.1±11.7 years of age, completed the study and provided all of the required information for this trial.

The basic therapeutic schemes where a combination of a diuretic with either an angiotensin-converting enzyme inhibitor (34.4% of the patients) or an angiotensin II receptor blocker (65.6% of the patients). The third drug was a dihydropyridine calcium channel blocker (CCB; 52.8% of the patients; mainly amlodipine or nifedipine gastrointestinal therapeutic system) or an α-blocker (always doxazosin gastrointestinal therapeutic system; 47.2% of the patients; Table 1).

After providing informed consent to participate in this prospective, randomized, open-label, blinded end point, parallel-group chronotherapy trial, patients were randomly assigned to 1 of 2 groups according to the modification in their treatment strategy: change of chronotherapy trial, patients were randomly assigned to 1 of 2 groups (Table 1). The third drug was a dihydropyridine calcium channel blocker (CCB; 52.8% of the patients; mainly amlodipine or nifedipine gastrointestinal therapeutic system) or an α-blocker (always doxazosin gastrointestinal therapeutic system; 47.2% of the patients; Table 1).

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ABPM Assessment
The SBP, DBP, and heart rate (HR) of each participant were automatically measured every 20 minutes from 7 AM to 11 PM and every 30 minutes during the night for 48 consecutive hours, before and after timed therapy, with a properly calibrated SpaceLabs 90207 device (SpaceLabs Inc). Participants were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM and to avoid daytime napping. BP series were not considered valid for analysis if >30% of the measurements were lacking, if they had missing data for >2-hour spans, or if measurements were collected from subjects while experiencing an irregular rest-activity schedule or a nighttime sleep span <6 hours or >12 hours during monitoring. Protocol-correct data series were collected from 250 subjects and, therefore, included in this efficacy study.

Statistical Methods
BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers. For descriptive purposes, the circadian rhythm of BP, HR, and wrist activity before and after treatment was objectively assessed by population multiple-component analysis. The daily (24-hour), diurnal (active-span), and nocturnal (resting-span) means of BP were further compared among groups by ANOVA. The demographic and clinical characteristics in Table 1 were compared among groups by ANOVA (quantitative variables) or nonparametric χ² test. Comparisons within each treatment group for each variable included in Table 1 measured before and after 3 months of intervention were performed by paired t test.

Results
Demographic Characteristics and Analytical Parameters
The baseline physical characteristics of the 2 groups of subjects (Table 1) were similar, and they remained unchanged after treatment. Clinic BP measurements, including pulse pressure (difference between SBP and DBP), were unchanged with all of the drugs on awakening. Clinic SBP and DBP were slightly but significantly reduced in patients treated with 1 drug at bedtime. There were no differences between treatment groups in the effects on clinic BP after correcting for baseline values (Table 1). The serum values of glucose, creatinine, uric acid, cholesterol, triglycerides (Table 1), and other laboratory chemistry variables of the 2 treatment groups were comparable at baseline and were not significantly changed after treatment.

Group 1: 3 Drugs on Awakening
Figure 1 (left) shows the circadian rhythm of SBP and DBP measured by 48-hour ABPM before and after treatment with all of the drugs on awakening. The dark shading along the lower horizontal axis of the graphs represents the average hours of nocturnal sleep across the patients. Results did not vary between the 2 consecutive days of sampling. Therefore, we decided to pool the BP data over an idealized single 24-hour profile to simplify the graphic display of the results. There was no change in BP after 3 months of treatment with a new therapeutic scheme but keeping the administration time of all of the drugs on awakening. After treatment, only 1 patient in this group showed controlled values of ABPM below the diagnostic thresholds mentioned above. The graphs on the left of Figure 1 show a marked nondipper pattern before treatment (here defined as patients with <10% decline in nocturnal mean
compared with the diurnal mean, the diurnal/nocturnal ratio, of BP using all of the data sampled by ABPM for 48 consecutive hours). Results in Table 2 indicate that 79% of the patients were nondipper before intervention and 86% were nondipper after intervention. HR remained unchanged after treatment (decrease in the 24-hour mean of 0.8 bpm; \(P=0.166\)). The circadian pattern of activity measured by wrist actigraphy also remained unchanged (\(P=0.316\) for comparison of 24-hour mean activity before and after treatment). The average duration of nocturnal rest was not statistically different for the profiles obtained before and after intervention (\(P=0.434\); Table 2).

<table>
<thead>
<tr>
<th>Group 2: 2 Drugs on Awakening and 1 Drug at Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>The graphs on the right in Figure 1 show the significant reduction in SBP (top) and DBP (bottom) after 3 months of</td>
</tr>
</tbody>
</table>
intervention with 2 drugs on awakening and a third one at bedtime. The BP reduction after treatment was statistically significant ($P < 0.05$ after correcting for multiple testing) in most of the 24 hourly intervals, as shown by the asterisks above the lower horizontal axis in the right panels of Figure 1. In keeping with the ABPM criteria mentioned above, 37% of the patients in this group had controlled BP after treatment. Figure 1 also indicates that the effect of this timed treatment was larger on the nocturnal than on the diurnal mean of BP. The circadian amplitude of BP was doubled after treatment ($P < 0.001$). Before intervention, 84% of the patients in this group were nondippers. This percentage was significantly reduced to 43% after intervention ($P < 0.001$; Table 2). Treatment with 1 of the drugs at bedtime also significantly reduced ambulatory pulse pressure (4 mm Hg reduction in 24-hour mean; $P < 0.001$). Despite the significant effect on BP, HR remained unchanged after 3 months of treatment (decrease in the 24-hour mean of 0.7 bpm; $P = 0.402$). The circadian pattern of wrist activity was also similar before and after 3 months of therapy ($P = 0.576$ for comparison of 24-hour mean activity). Average duration of nocturnal rest determined by actigraphy was not statistically different ($P = 0.132$) for the profiles obtained before and after intervention (Table 2). The number of patients with an extreme-dipper pattern (diurnal:nocturnal ratio $>20$%) was slightly increased from 3 to 6 ($P = 0.309$).

Comparison Between Groups
Comparison of the results shown in Figure 1 reveals a lack of statistically significant differences in ambulatory BP at baseline among the treatment groups (Table 2). After 3 months of timed treatment, there were statistically significant differences between treatment groups in both absolute and relative changes from baseline in the diurnal, nocturnal, and 24-hour mean of BP (Table 2). Figure 2 provides additional information on the comparison between the treatment groups of the changes in the diurnal, nocturnal, and 24-hour mean BP values after therapy. Results indicate the lack of any significant change in BP after treatment with 3 drugs on awakening. Figure 2 also indicates that, when one of the drugs was administered at bedtime, the effect on BP was 3 times larger on the nocturnal than on the diurnal mean of BP (Table 2). Accordingly, the diurnal:nocturnal BP ratio (an index of BP dipping) was significantly increased by 7.2% only when 1 drug was administered at bedtime but not when all of the drugs were administered in a single morning dose.

Results from ANOVA further indicate that the significant effects on BP were similar for each of the 4 subgroups of patients treated with 1 drug at bedtime, divided according to their baseline therapeutic combination (diuretic with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus CCB or $\beta$-blocker; $P > 0.638$ for the difference of effects among groups in the diurnal, nocturnal, and 24-hour mean of SBP and DBP). Figure 3, eg, shows the
comparative efficacy on SBP for each of the 4 subgroups of patients of either keeping all of the drugs on awakening (top; no effect on BP for any subgroup) or moving 1 of the drugs to be ingested at bedtime (bottom; significant BP reduction after treatment with the new therapeutic scheme; \( P<0.001 \) independent of drug combination).

**Discussion**

Results from this prospective trial indicate that patients with true resistant hypertension (based on ABPM criteria) who were assigned to receive 1 of their 3 prescribed antihypertensive drugs at bedtime presented ambulatory BP measurements significantly below baseline values after intervention. The reduction in BP resulted in 37% of these patients being controlled after 3 months of intervention with the new therapeutic scheme. On the contrary, only 1 of the 125 patients who were still receiving all of the drugs on awakening had a controlled ambulatory BP after intervention. A previous study on a small number of patients with resistant hypertension has also suggested that a combination of ABPM with chronotherapy, by administering drugs at times of the day synchronized with peaks of BP, was recommended for increasing BP control.\(^7\) Results lead the author to postulate that the concept of resistant hypertension should be modified to specifically incorporate, after stating uncontrolled BP after treatment with \( \geq 3 \) drugs, "administered with chronotherapeutic criteria."\(^7\)

Results from Table 2 indicate a high prevalence of an altered nondipper profile in BP at baseline in both treatment time groups of patients with resistant hypertension. Such high prevalence of nondipping was noted previously in another study on the 24-hour pattern of ABPM in

Table 2. Ambulatory BP Characteristics of Subjects Investigated

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Drugs on Awakening</th>
<th>1 Drug at Bedtime</th>
<th>( P ) for Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>125</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Before treatment, mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal rest, h</td>
<td>9.1±1.2 (0.434)</td>
<td>9.0±1.0 (0.132)</td>
<td>0.840</td>
</tr>
<tr>
<td>Diurnal mean of SBP, mm Hg</td>
<td>137.3±14.5 (0.978)</td>
<td>133.4±15.9 (&lt;0.001)</td>
<td>0.024</td>
</tr>
<tr>
<td>Nocturnal mean of SBP, mm Hg</td>
<td>134.1±16.9 (0.251)</td>
<td>120.7±17.2 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean of SBP, mm Hg</td>
<td>136.3±14.3 (0.690)</td>
<td>129.2±15.8 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day:night ratio of SBP, %</td>
<td>2.1±9.1 (0.156)</td>
<td>9.4±8.5 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diurnal mean of DBP, mm Hg</td>
<td>80.3±12.5 (0.293)</td>
<td>79.3±10.6 (&lt;0.001)</td>
<td>0.508</td>
</tr>
<tr>
<td>Nocturnal mean of DBP, mm Hg</td>
<td>73.8±11.9 (0.274)</td>
<td>67.2±9.4 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean of DBP, mm Hg</td>
<td>78.1±12.0 (0.716)</td>
<td>75.3±9.8 (&lt;0.001)</td>
<td>0.046</td>
</tr>
<tr>
<td>Day:night ratio of DBP, %</td>
<td>7.7±8.4 (0.019)</td>
<td>14.9±8.5 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nondipper, %</td>
<td>86.4 (0.131)</td>
<td>43.2 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Average % reduction from baseline, mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diurnal mean of SBP</td>
<td>-0.3±8.4</td>
<td>4.1±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nocturnal mean of SBP</td>
<td>-1.3±8.8</td>
<td>10.9±9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean of SBP</td>
<td>-0.5±7.8</td>
<td>6.4±8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diurnal mean of DBP</td>
<td>0.5±7.1</td>
<td>4.3±9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nocturnal mean of DBP</td>
<td>-1.5±9.8</td>
<td>11.7±10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean of DBP</td>
<td>0.1±7.1</td>
<td>6.9±8.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The day:night ratio, an index of the BP dipping, is defined as the percentage of decline in BP during hours of nocturnal rest relative to the mean BP obtained during the hours of diurnal activity. Nondipper indicates <10% decline in nocturnal mean compared with the diurnal mean of SBP using data sampled by ABPM for 48 consecutive hours.
resistant hypertension. In this trial, patients with true resistant hypertension showed an even higher nocturnal mean of BP and a higher prevalence of nondipping than patients with white-coat resistant hypertension. No attention was paid in this trial, however, to the time of antihypertensive treatment. In a previous cross-sectional epidemiologic study, we found a significant reduction from 82% to 57% in the prevalence of nondipping when patients with true resistant hypertension who received all of the prescribed drugs on awakening were compared with an independent sample of patients who were taking 1 drug at bedtime. Results from the present prospective intervention study (Figure 1) indicate that the beneficial effect of a new therapeutic scheme consisting of administering 1 drug at bedtime was markedly larger in the nocturnal than in the diurnal mean of BP. This timed therapy thus resulted in a significant reduction from 84% to 43% in the prevalence of nondipper patients after intervention (Table 2). The potential relationship between the increased prevalence of nondipper patients and cardiovascular risk has not been prospectively investigated in resistant hypertension. Although the mechanism underlying the lack of nocturnal decline in BP is unclear, nondipping has been related to an increase in end-organ injury and cardiovascular events. Moreover, several independent prospective studies have concluded that nighttime BP is a better predictor of cardiovascular mortality than the diurnal or the 24-hour means. Figure 1, in agreement with previous epidemiologic studies, shows the diminished nocturnal BP decline that characterizes most patients with resistant hypertension.

The potential reduction in cardiovascular risk associated with the normalization of the circadian variability of BP (converting a nondipper to dipper pattern) has not yet been fully established. Apart from the Syst-Eur Trial, where nitrendipine was dosed at bedtime, results from the HOPE substudy where patients were evaluated by ABPM indicated a significant BP reduction mainly during hours of nighttime sleep. The authors suggested that the beneficial effects on cardiovascular morbidity and mortality in the Heart Outcomes Prevention Evaluation Study may be related to the 8% increase in the diurnal: nocturnal ratio of BP seen after ramipril was administered at bedtime. Moreover, a recent prospective trial has demonstrated that increasing the diurnal: nocturnal BP ratio with bedtime administration of valsartan was markedly correlated with a significant decrease in urinary albumin excretion. Evaluation of a potential decrease in cardiovascular risk, as well as the impact of timed treatment on surrogate measures of risk in patients with resistant hypertension, deserves further prospective investigation. In any event, international guidelines provide reference thresholds for ABPM, including normal limits for diurnal and nocturnal BP. In this trial, the percentage of patients with controlled diurnal and nocturnal BP was significantly increased from 0.8% to 37% \( (P<0.001) \) when 1 of the 3 prescribed drugs was administered at bedtime.
Appreciable ingestion time differences in the kinetics (ie, chronokinetics) of BP-lowering and cardiac medications are well known.\textsuperscript{22} Clinically relevant dosing time differences in the beneficial and adverse effects (termed “chronodynamics”) of BP-lowering medications are also known.\textsuperscript{23} However, in spite of the great number of published evaluations of antihypertension medications, rarely has the time of day of drug administration been a specific focus of investigation.\textsuperscript{10,24} In this study, apart from the added change in administration time in 1 treatment group, we mainly interchanged a CCB and an \( \alpha \)-blocker. Although not all of the CCBs exhibit dosing time differences in effects,\textsuperscript{24} Portaluppi et al\textsuperscript{25} explored the advantage of evening versus morning once-a-day treatment with isradipine on the nondipping 24-hour pattern of BP in patients with chronic renal failure. The findings of this study demonstrated that an evening, as compared with a morning, isradipine treatment schedule is more likely to effectively reduce the 24-hour mean SBP and DBP and restore the normal nocturnal dipping and circadian BP patterning. In another recent trial, 60 mg/d of the gastrointestinal therapeutic system formulation of nifedipine were significantly more effective when administered at bedtime than on awakening in patients with essential hypertension, whereas also significantly reducing the prevalence of secondary effects.\textsuperscript{26} On the other hand, a recent study exploring the administration time-dependent effects of doxazosin GITS indicated that administration of the drug on awakening failed to provide full 24-hour therapeutic coverage, whereas bedtime dosing significantly reduced BP throughout the entire 24 hours, whether used alone as a monotherapy or in combination with other antihypertensive pharmacotherapy.\textsuperscript{27} Studies on the potential administration time-dependent effects of other antihypertensive drugs in combination therapy are still lacking and deserve further investigation.

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**Disclosures**

None.

**References**


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