

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 (9.4/6.0 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 hypertension^{5,6} 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.

Received June 25, 2007; first decision July 23, 2007; revision accepted October 8, 2007.

From the Bioengineering and Chronobiology Laboratories (R.C.H., D.E.A., J.R.F.), University of Vigo, Campus Universitario, Vigo, Spain; and the Hypertension and Vascular Risk Unit (C.C.), Hospital Clínico Universitario, Santiago de Compostela, Spain

Correspondence to Ramón C. Hermida, Bioengineering and Chronobiology Laboratories, ETSI Telecomunicación, Campus Universitario, Vigo (Pontevedra) 36200, Spain. E-mail rhermida@uvigo.es

© 2007 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.107.096933

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 \geq 140 mm Hg and/or DBP \geq 90 mm Hg).^{1,2,9} 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.^{2,9} Moreover, inclusion criteria required that patients were treated for \geq 3 months with a stable scheme consisting of 3 antihypertensive drugs in a single morning dose, with an adequate combination and dose.² 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 \pm 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 the third of the drugs mentioned above to a different one, thus maintaining a synergic combination² and still administering all 3 drugs on awakening or the same approach but administering the new drug at bedtime. The State Ethics Committee of Clínica Research approved the trial, part of the prospective Monitorización Ambulatoria de Presión Arterial y Eventos Cardiovasculares Study,¹⁰ mainly designed to investigate whether normalizing the circadian BP profile toward a more dipper pattern by time-specified treatment reduces cardiovascular risk.

Blood samples were obtained in the clinic from the antecubital vein after nocturnal fasting between 8 AM and 9 AM on the same days when 48-hour ABPM was initiated, both immediately before and after 3 months of intervention. Clinic BP measurements (6 per study visit after being seated for \geq 5 minutes on the same day just before starting ABPM) were always obtained by the same investigator with a validated automatic oscillometric device (HEM-737, Omron Health Care Inc).¹¹

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.

Actigraphy

Every participant wore a Mini-Motion-Logger actigraph (Ambulatory Monitoring Inc) on the dominant wrist to monitor physical activity every minute of the day and night throughout each 48-hour, ABPM session. The actigraphy data were used to determine the onset and offset times of diurnal activity and nocturnal sleep so as to accurately determine the diurnal and nocturnal BP means of each subject. The mean activity for the 5 minutes before each BP reading was then calculated for further statistical analysis of the circadian variability of activity level following previously established procedures.^{4,12}

Statistical Methods

BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers.¹³ For descriptive purposes, the circadian rhythm of BP, HR, and wrist activity before and after treatment was objectively assessed by population multiple-component analysis.¹⁴ 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 χ^2 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 in the morning. 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.^{2,9} 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

Table 1. Demographic and Analytical Characteristics of Subjects Investigated

Variable	All Drugs on Awakening	1 Drug at Bedtime	<i>P</i> for Group Comparison
Patients, n	125	125	
Baseline treatment schedule, n			
Diuretic	125	125	
ARB	81	83	
ACEI	44	42	
CCB	66	66	
α -Blocker	59	59	
Sex, % men	56.0	52.8	0.612
Age, mean \pm SD, y	60.0 \pm 11.6	60.1 \pm 11.9	0.928
Height, mean \pm SD, cm	160.6 \pm 9.8	159.0 \pm 10.1	0.179
Before treatment, mean \pm SD			
Weight, kg	77.6 \pm 14.5	77.9 \pm 16.2	0.862
BMI, kg/m ²	29.9 \pm 4.0	30.6 \pm 4.6	0.181
Clinic SBP, mm Hg*	158.4 \pm 18.8	160.5 \pm 23.3	0.519
Clinic DBP, mm Hg*	87.8 \pm 11.2	88.5 \pm 12.5	0.370
Clinic PP, mm Hg*	70.6 \pm 16.6	72.0 \pm 18.7	0.514
Glucose, mg/dL	123.3 \pm 48.7	121.0 \pm 38.8	0.699
Creatinine, mg/dL	1.01 \pm 0.33	0.99 \pm 0.24	0.445
Uric acid, mg/dL	5.7 \pm 1.7	5.8 \pm 1.7	0.700
Cholesterol, mg/dL	213.4 \pm 34.4	208.1 \pm 38.2	0.275
Triglycerides, mg/dL	116.4 \pm 52.7	106.9 \pm 60.1	0.325
After treatment (in parenthesis, <i>P</i> from comparison with values before treatment), mean \pm SD			
Weight, kg	77.5 \pm 14.6 (0.644)	78.1 \pm 16.6 (0.406)	0.712
BMI, kg/m ²	29.8 \pm 4.1 (0.641)	30.7 \pm 4.7 (0.429)	0.113
Clinic SBP, mm Hg*	154.1 \pm 19.8 (0.084)	154.6 \pm 21.6 (0.037)	0.846
Clinic DBP, mm Hg*	86.0 \pm 13.1 (0.262)	84.2 \pm 12.3 (0.007)	0.493
Clinic PP, mm Hg*	68.1 \pm 15.3 (0.057)	70.4 \pm 17.7 (0.209)	0.281
Glucose, mg/dL	118.5 \pm 41.5 (0.417)	118.6 \pm 35.4 (0.370)	0.984
Creatinine, mg/dL	1.06 \pm 0.35 (0.331)	1.02 \pm 0.30 (0.345)	0.375
Uric acid, mg/dL	6.0 \pm 1.5 (0.386)	5.8 \pm 1.4 (0.793)	0.243
Cholesterol, mg/dL	208.4 \pm 34.8 (0.271)	200.9 \pm 34.6 (0.147)	0.109
Triglycerides, mg/dL	102.4 \pm 48.5 (0.117)	101.4 \pm 47.1 (0.456)	0.877
Average % reduction from baseline, mean \pm SD			
Clinic SBP*	-1.9 \pm 1.2	-2.5 \pm 1.3	0.732
Clinic DBP*	-1.6 \pm 1.1	-3.8 \pm 1.2	0.177
Clinic PP*	-1.2 \pm 1.8	-1.4 \pm 1.8	0.648

PP indicates pulse pressure; BMI, body mass index; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

*Values correspond with the average of 6 conventional BP measurements obtained on each subject in the clinic before commencing 48 hours of ABPM.

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).

Group 2: 2 Drugs on Awakening and 1 Drug at Bedtime

The graphs on the right in Figure 1 show the significant reduction in SBP (top) and DBP (bottom) after 3 months of

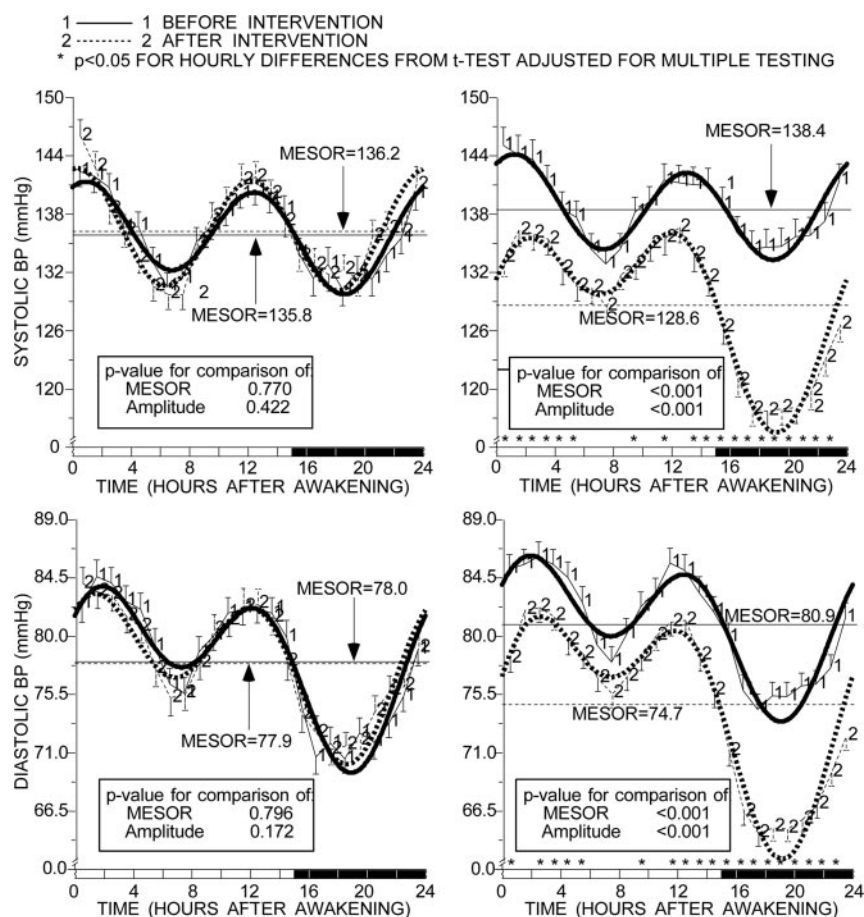


Figure 1. Circadian pattern of SBP (top) and DBP (bottom) before (continuous line) and after (dashed line) 3 months of therapy in patients with resistant hypertension receiving 3 antihypertensive drugs on awakening (left) or receiving 2 drugs on awakening and 1 drug at bedtime (right). Dark shading along the lower horizontal axis of the graphs represents average hours of nocturnal sleep across the patients. The nonsinusoidal-shaped curves represented around means and SEs correspond with the best-fitted waveform model determined by population multiple-component analysis. Midline estimating statistic of rhythm (MESOR) is the average value of the rhythmic function fitted to the data. Amplitude is one half the difference between the maximum and minimum values of the best-fitted curve.

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:nightly 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:nightly 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 α -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

Table 2. Ambulatory BP Characteristics of Subjects Investigated

Variable	All Drugs on Awakening	1 Drug at Bedtime	<i>P</i> for Group Comparison
Patients, n	125	125	
Before treatment, mean±SD			
Nocturnal rest, h	9.1±1.2	8.9±1.3	0.175
Diurnal mean of SBP, mm Hg	137.2±13.0	139.6±16.5	0.203
Nocturnal mean of SBP, mm Hg	132.9±16.6	136.1±18.7	0.149
24-h mean of SBP, mm Hg	135.9±13.1	138.6±16.3	0.141
Day:night ratio of SBP, %	3.0±9.6	2.4±9.2	0.562
Diurnal mean of DBP, mm Hg	80.8±12.1	83.3±11.6	0.095
Nocturnal mean of DBP, mm Hg	73.1±12.2	76.6±10.2	0.152
24-h mean of DBP, mm Hg	78.3±11.7	81.3±10.7	0.135
Day:night ratio of DBP, %	9.6±8.8	7.7±9.3	0.129
Nondipper, %	79.2	84.0	0.327
After treatment (in parenthesis, <i>P</i> from comparison with values before treatment), mean±SD			
Nocturnal rest, h	9.0±1.2 (0.434)	9.0±1.0 (0.132)	0.840
Diurnal mean of SBP, mm Hg	137.3±14.5 (0.978)	133.4±15.9 (<0.001)	0.024
Nocturnal mean of SBP, mm Hg	134.1±16.9 (0.251)	120.7±17.2 (<0.001)	<0.001
24-h mean of SBP, mm Hg	136.3±14.3 (0.690)	129.2±15.8 (<0.001)	<0.001
Day:night ratio of SBP, %	2.1±9.1 (0.156)	9.4±8.5 (<0.001)	<0.001
Diurnal mean of DBP, mm Hg	80.3±12.5 (0.293)	79.3±10.6 (<0.001)	0.508
Nocturnal mean of DBP, mm Hg	73.8±11.9 (0.274)	67.2±9.4 (<0.001)	<0.001
24-h mean of DBP, mm Hg	78.1±12.0 (0.716)	75.3±9.8 (<0.001)	0.046
Day:night ratio of DBP, %	7.7±8.4 (0.019)	14.9±8.5 (<0.001)	<0.001
Nondipper, %	86.4 (0.131)	43.2 (<0.001)	<0.001
Average % reduction from baseline, mean±SD			
Diurnal mean of SBP	−0.3±8.4	4.1±8.6	<0.001
Nocturnal mean of SBP	−1.3±8.8	10.9±9.4	<0.001
24-h mean of SBP	−0.5±7.8	6.4±8.1	<0.001
Diurnal mean of DBP	0.5±7.1	4.3±9.8	<0.001
Nocturnal mean of DBP	−1.5±9.8	11.7±10.1	<0.001
24-h mean of DBP	0.1±7.1	6.9±8.9	<0.001

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.

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 ≥ 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

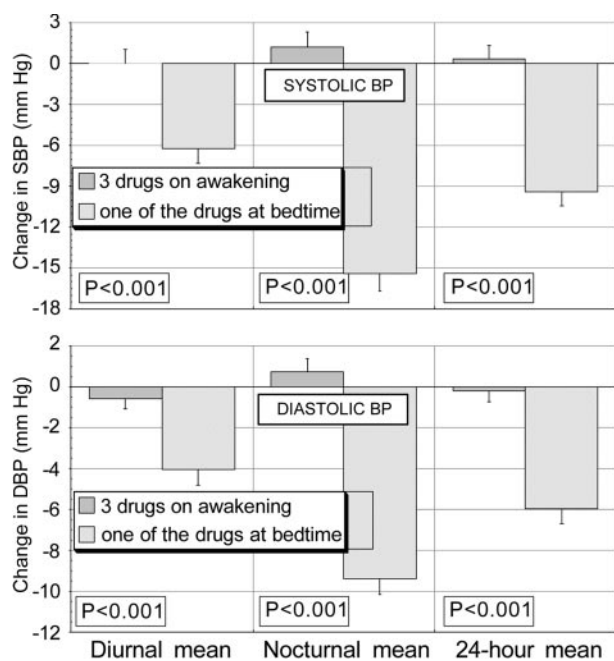


Figure 2. Changes (in millimeters of mercury) in the diurnal (active hours), nocturnal (sleep time), and 24-hour mean of SBP (top) and DBP (bottom) after 3 months of therapy in patients with resistant hypertension receiving 3 antihypertensive drugs on awakening or receiving 2 drugs on awakening and 1 drug at bedtime. *P* values are shown for comparison of effects between the 2 groups of subjects by ANOVA.

resistant hypertension.⁶ 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.⁶ 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.⁸

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.^{15–17} 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.^{16,18,19} Figure 1, in agreement with previous epidemiologic studies,^{6,8} shows the

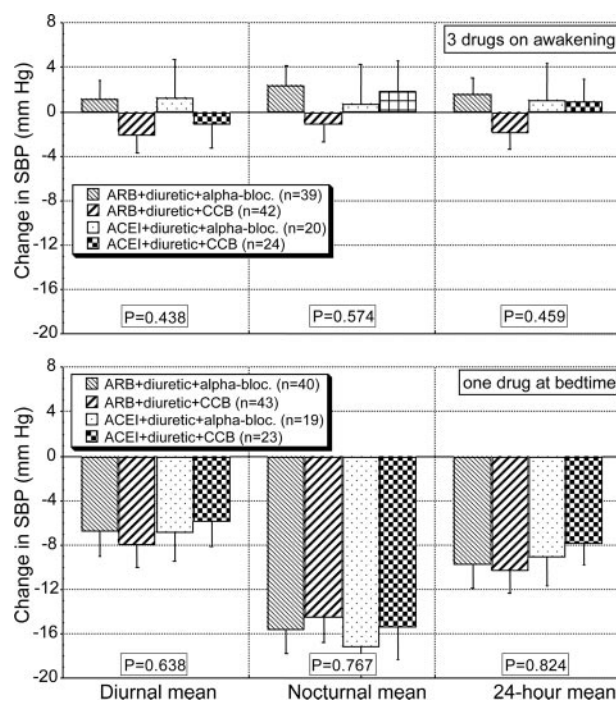


Figure 3. Changes (in millimeters of mercury) in the diurnal (active hours), nocturnal (sleep time), and 24-hour mean of SBP after 3 months of therapy in patients with resistant hypertension receiving 3 antihypertensive drugs on awakening (top) or receiving 2 drugs on awakening and 1 drug at bedtime (bottom), according to their baseline drug combination. *P* values are shown for the comparison of effects among the 4 groups of subjects by ANOVA. Numbers in parenthesis in the legend indicate the number of patients in each subgroup.

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.¹⁰ Apart from the Syst-Eur Trial, where nitrendipine was dosed at bedtime,¹⁶ results from the HOPE substudy where patients were evaluated by ABPM indicated a significant BP reduction mainly during hours of nighttime sleep.²⁰ 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.²¹ 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.^{1,2,9} 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.²² Clinically relevant dosing time differences in the beneficial and adverse effects (termed “chronodynamics”) of BP-lowering medications are also known.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.^{10,24} In this study, apart from the added change in administration time in 1 treatment group, we mainly interchanged a CCB and an α -blocker. Although not all of the CCBs exhibit dosing time differences in effects,²⁴ Portaluppi et al²⁵ 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.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.²⁷ Studies on the potential administration time-dependent effects of other antihypertensive drugs in combination therapy are still lacking and deserve further investigation.

Perspectives

Results from this prospective chronotherapy trial on patients with resistant hypertension indicate that time of treatment in relation to the rest-activity cycle of each individual subject may be more important for BP control and for the proper modeling of the circadian BP pattern than just changing the drug combination. This approach also allows a large percentage of the patients to revert the highly prevalent nondipper BP pattern to a dipper profile. Whether this normalization of the BP pattern could also decrease cardiovascular risk in patients with resistant hypertension, beyond the expected reduction in risk derived from lowering BP mean values, is a hypothesis that merits investigation.

Sources of Funding

This independent investigator-promoted research was supported in part by grants from Dirección General de Investigación, Ministerio de Educación y Ciencia (SAF2006-6254), Xunta de Galicia (PGIDIT03-PXIB-32201PR), Hospital Clínico Universitario de Santiago, and Vicerrectorado de Investigación, University of Vigo.

Disclosures

None.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Rocella EJ, and the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
2. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 guidelines for the management of arterial hypertension. *J Hypertens*. 2007;25:1105–1187.
3. Cuspidi C, Macca G, Sampieri L, Michev I, Salerno M, Fusi V, Severgnini B, Meani S, Magrini F, Zanchetti A. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens*. 2001;19:2063–2070.
4. Hermida RC, Calvo C, Ayala DE, Mojón A, López JE. Relationship between physical activity and blood pressure in dipper and nondipper hypertensive patients. *J Hypertens*. 2002;20:1097–1104.
5. Veglio F, Rabbia F, Riva P, Martini G, Genova GC, Lilan A, Paglieri C, Carra R, Chiandissi L. Ambulatory blood pressure monitoring and clinical characteristics of the true and white-coat resistant hypertension. *Clin Exp Hypertens*. 2001;23:203–211.
6. Muxfeldt ES, Bloch KV, Nogueira AR, Salles GF. Twenty-four hour ambulatory blood pressure monitoring pattern of resistant hypertension. *Blood Press Monit*. 2003;8:181–185.
7. Cugini P. The treatability of refractory or resistant hypertension by personalized antihypertensive chronotherapy based on ambulatory monitoring of the arterial pressure. *Recenti Prog Med*. 1996;87:51–57.
8. Hermida RC, Ayala DE, Calvo C, López JE, Mojón A, Fontao MJ, Soler R, Fernández JR. Effects of the time of day of antihypertensive treatment on the ambulatory blood pressure pattern of patients with resistant hypertension. *Hypertension*. 2005;46:1053–1059.
9. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Rocella EJ. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans. *Hypertension*. 2005;45:142–161.
10. Hermida RC, for the MAPEC Study Investigators. Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC study. *Chronobiol Int*. 2007;24:749–775.
11. Anwar YA, Giacco S, McCabe EJ, Tendler BE, White WB. Evaluation of the efficacy of the Omron HEM-737 Intellisense device for use on adults according to the recommendations of the Association for the Advancement of Medical Instrumentation. *Blood Press Monit*. 1998;3:261–265.
12. Mansoor GA, White WB, McCabe EJ, Giacco S. The relationship of electronically monitored physical activity to blood pressure, heart rate, and the circadian blood pressure profile. *Am J Hypertens*. 2000;13:262–267.
13. Staessen J, Fagard R, Lijnen P, Thijs L, Vaa Hoof R, Amery A. Ambulatory blood pressure monitoring in clinical trials. *J Hypertens*. 1991;9(suppl 1):s13–s19.
14. Fernández JR, Hermida RC. Inferential statistical method for analysis of nonsinusoidal hybrid time series with unequidistant observations. *Chronobiol Int*. 1998;15:191–204.
15. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension*. 1994;24:793–801.
16. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*. 1999;282:539–546.
17. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens*. 2002;20:2183–2189.

18. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.
19. Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality. The Ohasama Study. *Hypertension*. 2005;45:240–245.
20. Svensson P, de Faire U, Sleight P, Yusuf S, Östergren J. Comparative effects of ramipril on ambulatory and office blood pressures. A HOPE substudy. *Hypertension*. 2001;38:e28–e32.
21. Hermida RC, Calvo C, Ayala DE, López JE. Decrease in urinary albumin excretion associated to the normalization of nocturnal blood pressure in hypertensive subjects. *Hypertension*. 2005;46:960–968.
22. Lemmer B. Cardiovascular chronobiology and chronopharmacology. Importance of timing of dosing. In: White WB, ed. *Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*. Totowa, NJ: Humana Press; 2000:255–271.
23. Witte K, Lemmer B. Rhythms and pharmacodynamics. In: Redfern P, ed. *Chronotherapeutics*. London, UK: Pharmaceutical Press; 2003: 111–126.
24. Hermida RC, Ayala DE, Calvo C. Administration time-dependent effects of antihypertensive treatment on the circadian pattern of blood pressure. *Curr Opin Nephrol Hypertens*. 2005;14:453–459.
25. Portaluppi F, Vergnani L, Manfredini R, degli Uberti EC, Fersini C. Time-dependent effect of isradipine on the nocturnal hypertension in chronic renal failure. *Am J Hypertens*. 1995;8:719–726.
26. Hermida RC, Calvo C, Ayala DE, López JE, Rodríguez M, Chayán L, Mojón A, Fontao MJ, Fernández JR. Dose and administration-time-dependent effects of nifedipine GITS on ambulatory blood pressure in hypertensive subjects. *Chronobiol Int*. 2007;24:471–493.
27. Hermida RC, Calvo C, Ayala DE, Domínguez MJ, Covelo M, Fernández JR, Fontao MJ, López JE. Administration-time-dependent effects of doxazosin GITS on ambulatory blood pressure of hypertensive subjects. *Chronobiol Int*. 2004;21:469–484.

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

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

Hypertension. 2008;51:69-76; originally published online October 29, 2007;

doi: 10.1161/HYPERTENSIONAHA.107.096933

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2007 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/51/1/69>

Data Supplement (unedited) at:

<http://hyper.ahajournals.org/content/suppl/2007/10/19/HYPERTENSIONAHA.107.096933.DC1.html>

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/>