Effects of chronotherapy on blood pressure control in non-dipper patients with refractory hypertension

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Abstract
Background. Refractory arterial hypertension (RAH) is frequently associated to a non-dipping blood pressure (BP) pattern; this profile has been shown to have a worse clinical prognosis. It is a common clinical practice that patients receive anti-hypertensive medication preferentially in the morning. Non-dipping could be related to the timing of anti-hypertensive drug administration. We analysed whether switching anti-hypertensive medication to bedtime could improve BP control in non-dipper patients with RAH.

Methods. Twenty-seven consecutive patients with RAH and non-dipper or riser BP pattern on ambulatory blood pressure (ABP) monitoring were studied before and after 6 weeks of a change in the timing of anti-hypertensive medications. The intervention consisted of shifting all non-diuretic anti-hypertensive drugs from morning to evening, maintaining the same drugs at the same doses. A parallel group of 12 consecutive patients with similar characteristics and no changes in the therapeutic regimen formed the control group.

Results. There were 59% women, mean age 65.7 ± 8.4 years. They were treated with 4 ± 0.7 anti-hypertensive drugs, 90% administered in the morning. At baseline, diurnal and nocturnal ABP averaged 141.6 ± 10.6/81.5 ± 9.3 and 141.7 ± 11/78 ± 8.8, respectively. After the drug shift, mean diurnal and nocturnal ABP was 140.5 ± 10.4/80.5 ± 9.6 and 135.7 ± 12.5/73.8 ± 9.3 (P = 0.005 and 0.04 for systolic and diastolic ABP), 15% of the patients restored a normal ABP circadian rhythm. No changes were observed in the control group.

Conclusion. In non-dipper or riser patients with RAH, changing the timing of anti-hypertensive medication to the evening could improve BP control.

Keywords: ambulatory blood pressure monitoring; chronotherapy; circadian rhythm; non-dipper; refractory hypertension

Introduction

Ambulatory blood pressure (ABP) monitoring is a useful tool in the evaluation of refractory arterial hypertension (RAH); it also provides information about blood pressure (BP) circadian rhythm [1]. Patients with RAH often present a non-dipper or riser pattern that has been associated with a higher cardiovascular risk and a higher prevalence of target organ damage [2, 3]. Furthermore, there is evidence that coronary and cerebrovascular events reach a maximum incidence in the morning, possibly in relation to the sudden rise of BP observed on awakening together with the rise in platelet aggregability, the sympathetic activation and the decrease of the fibrinolytic activity [4–11]. All this suggests that the potential interest of interventions addressed not only to lower BP levels but also to improve BP circadian rhythm. Following the previous rationale, several recent papers have introduced the concept of chronotherapy after studying the effects of changes in the timing of anti-hypertensive drug intake on circadian BP pattern. These papers showed an improvement in both the BP morning surge and BP control [12–23]. Some of these studies have pointed to a potential role of chronotherapy in the therapy of RAH [19, 23].

This prospective, before and after, observational study aims to evaluate the effect of chronotherapy adjustment on BP control and BP circadian rhythm in non-dipper patients with RAH. The intervention consisted of modifying the time of treatment, without increasing the number or doses of the drugs, shifting all anti-hypertensive medication except the diuretic to bedtime.

Materials and methods

Eligible patients were >18 years, received health care for hypertension in the Nephrology Services of either Corporació Parc Taulí or Hospital General de Vic. The study was approved by the Ethical Committee of Clinical Research of both hospitals. All patients were informed about the study protocol and gave their written informed consent before study enrolment.

Enrolment was based on the following inclusion criteria: (i) treatment with three or more anti-hypertensive drugs, which always included a full
dose diuretic, for at least 3 months; (ii) average systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) >90 mmHg during the previous 3 months; (iii) administration of ≥75% of the anti-hypertensive medication in the morning; (iv) a pre-intervention ABP showing a non-dipper or riser profile and either a 24-h mean SBP/DBP ≥130/80 mmHg a diurnal (awake) mean SBP/DBP ≥135/85 mmHg or a nocturnal (sleep time) mean of SBP/DBP ≥120/70 mmHg. Non-dipper status was defined as a night/day ratio SBP on ABP >0.9.

Patients were excluded if they met any of the following conditions: SBP/DBP mean in the activity period ≥155/105 mmHg; a dipper pattern in the ABP; unstable medical situation; coronary heart disease, stroke or another cardiovascular event in the last 6 months; onset atrial fibrillation; poor adherence to therapy according to the Haynes–Sackett test or patients who missed at least one of the scheduled visits in the last year; working night shifts and change in the type or dosage of anti-hypertensive medication between both ABP.

In all patients, a chronotherapeutic adjustment of the anti-hypertensive drugs was carried out, which consisted of maintaining the same anti-hypertensive drugs and the same doses, moving its administration to bedtime, except diuretics, which were always taken in the morning. This change was registered in the medication prescription sheet given to patients to facilitate adherence. Six weeks (±1 week) after the chronotherapeutic intervention, a second ABP was performed.

A parallel group of 12 consecutive patients, with similar clinical characteristics (RAH and non-dipper or riser BP pattern on ABP), in whom no changes in the therapeutic regimen were made, was studied before and after 6 weeks and formed the control group.

The mean number of anti-hypertensive agents prescribed to the study group was 4 ± 0.7; 90% administered in the morning. The control group was treated with 3.8 ± 0.6 anti-hypertensive agents, 64% administered in the morning.

ABP were carried out with a properly calibrated SpaceLabs 90207 device (SpaceLabs Inc., Redmond, WI). SBP and DBP were automatically measured and recorded every 20 min during the day and every 30 min at night. Patients were instructed to fill in a diary of activities indicating the times of getting up and going to bed, in order to determine later the activity and rest periods, as well as any other incidences which could affect their BP. Patients in whom ABP monitoring showed <70% of valid BP readings or more than three consecutive hours without any BP measurement were excluded from the study [24]. Depth was calculated as the difference between average diurnal and nocturnal BP.

The morning BP surge was calculated as the morning BP minus the lowest BP. Morning BP was defined as the average BP during the first 2 h after waking. The lowest BP was defined as the average of three BP readings focused on the lowest night-time reading (that is, the lowest reading plus the readings immediately before and after) [7].

![Fig. 1. SBP on ABP monitoring at baseline (A) and after the drug shift (B). * = 0.031; ** = 0.005.](image)

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 27)</th>
<th>Control group (n = 12)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>65.6 ± 8.4</td>
<td>62.6 ± 6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex: women (%)</td>
<td>16 (59.3)</td>
<td>6 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (18.5)</td>
<td>1 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.0 ± 5.2</td>
<td>34.7 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>122 ± 33</td>
<td>129 ± 37</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>58 ± 23</td>
<td>84 ± 26</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>185 ± 36</td>
<td>181 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>48 ± 11</td>
<td>45 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>114 ± 32</td>
<td>108 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria (g/24-h)</td>
<td>0.32 ± 0.47</td>
<td>0.26 ± 0.32</td>
<td>NS</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>15 (56)</td>
<td>10 (83)</td>
<td>0.1 (NS)</td>
</tr>
<tr>
<td>Family history of CV disease</td>
<td>4 (15)</td>
<td>2 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (26)</td>
<td>6 (50)</td>
<td>0.15 (NS)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>9 (36)</td>
<td>4 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2 (7.4)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5 (18.5)</td>
<td>1 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1 (3.7)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Hypotensive drugs (number)</td>
<td>4.0 ± 0.7</td>
<td>3.8 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data shown as mean ± SD or number (%); BMI, body mass index; CV, cardiovascular; MDRD, Modification of Diet in Renal Disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
All statistical analysis was performed using SPSS v.18.0 for Windows. The continuous variables are shown as the mean (SD) and the categorical ones as the number of subjects and the percentage (%). The 24-h, the nocturnal and diurnal BP means after the intervention were compared to the baseline BP means by a t-Student's for paired samples. In the case of variables not following a normal distribution, we used the non-parametric test of Wilcoxon for paired samples. To determine the circadian profiles, the registered times of the BP values were synchronized for each patient and the clock hours were transformed into hours gone by/taken place since the moment of waking up. Significance was set at 0.05.

**Sample size power calculation**

We estimated that a minimum of 23 patients were necessary to detect a decrease in the SBP after chronotherapy of at least 6 mmHg using a paired t-test with one tailed a = 0.05 and a power of 0.80 assuming a SD of the differences of 11 mmHg based on previous observations by our group and others [25].

**Results**

Twenty-seven patients that met inclusion criteria and gave their informed consent to participate were included in the study. Patient and control group clinical characteristics are listed in Table 1.

At baseline, overall 24-h, diurnal and nocturnal ABP averaged 141.7 ± 9.8/80.4 ± 8.8; 141.6 ± 10.6/81.5 ± 9.3 and 141.7 ± 11/78 ± 8.8, respectively. After the drug shift, a BP decline was observed in all periods (overall, diurnal and nocturnal) of the second ABP, mean BP was 138.9 ± 9/78.3 ± 8.8; 140.5 ± 10.4/80.5 ± 9.6 and 135.7 ± 12.5/73.8 ± 9.3, respectively. However, the SBP differences only reach statistical significance (P < 0.05) for the overall and the nocturnal periods: 2.7 and 6.1 mmHg decrease, respectively (Figure 1). The same was true for the DBP with differences of 2 and 4.2 mmHg for the overall and nocturnal periods, respectively (P < 0.05) (Figure 2). The nocturnal ABP decrease was not associated with an increase in diurnal ABP values: the differences for the diurnal period were 1.1 and 1.0 mmHg decrease for the SBP and DBP, respectively [P = not significant (NS)]. No changes were observed in the control group (Table 2, Figures 1 and 2). Since there were some differences in renal function between the study and control groups, we analysed separately the response to chronotherapy categorizing patients with a creatinine clearance above or below than 60 mL/min/1.73m²; there was no difference in the response (data not shown).

**Table 2. BP differences obtained with the 95% confidence interval**

<table>
<thead>
<tr>
<th></th>
<th>Chronotherapy (n = 27)</th>
<th></th>
<th>Controls (n = 12)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP difference (a)</td>
<td>95% confidence interval for the differences</td>
<td>(p^b)</td>
<td>BP difference (a)</td>
</tr>
<tr>
<td>24-h SBP</td>
<td>-2.7 (6.2)</td>
<td>-5.1 to -0.3</td>
<td>0.03</td>
<td>+0.3 (11.4)</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>-2.0 (4.2)</td>
<td>-3.6 to -0.3</td>
<td>0.02</td>
<td>+1.4 (6.3)</td>
</tr>
<tr>
<td>Diurnal SBP</td>
<td>-1.2 (5.7)</td>
<td>-3.4 to 1.1</td>
<td>0.31</td>
<td>-0.3 (11.2)</td>
</tr>
<tr>
<td>Diurnal DBP</td>
<td>-1.0 (4.1)</td>
<td>-2.6 to +0.7</td>
<td>0.23</td>
<td>+1.7 (7.7)</td>
</tr>
<tr>
<td>Nocturnal SBP</td>
<td>-6.1 (10.4)</td>
<td>-10.1 to -2.0</td>
<td>0.005</td>
<td>+0.8 (13.8)</td>
</tr>
<tr>
<td>Nocturnal DBP</td>
<td>-4.2 (7.0)</td>
<td>-7.0 to -1.5</td>
<td>0.004</td>
<td>+1.1 (8.3)</td>
</tr>
</tbody>
</table>

\(a\)BP difference (in mmHg) = ABP2 − ABP1.

\(b\)P, paired t-test.
Hourly averages of ABP: Figure 4 shows the SBP and the DBP circadian pattern before and after the intervention. BP profiles at baseline and after the drug shift showed a similar trend during the day, but the decrease became apparent after 10–11 h PM.

A non-statistically significant decline of the morning BP surge was observed after the intervention: 2.2 and 0.5 mmHg for SBP and DBP, respectively.

Discussion

The results of the present study confirm the importance of chronotherapy as a strategy to improve BP control among patients with RAH. In particular, patients with a non-dipper or riser profile can benefit from this therapeutic approach.

In the last years, some studies have shown the potential role of the chronotherapy in improving BP circadian profile [14–18], attenuating BP morning surge [20, 21] and decreasing target organ damage [9–11, 13] and the co-morbidity associated with hypertension [7, 8, 22]. However, it is still common practice to advise patients to take their anti-hypertensive drugs in the morning. In general, the mainstream of previous studies has been performed on patients with essential hypertension treated with only one class of anti-hypertensive drug.

The mechanisms involved in the beneficial effects of chronotherapy are not well known, although they probably have to do with a better use of the pharmacokinetic properties of the drugs, allowing a peak in drug activity at night if the anti-hypertensive agents are administrated in the evening. Several other factors, such as circadian rhythms of gastric pH and emptying, biliary function and gastrointestinal motility and circulation, can substantially affect pharmacokinetics and the BP lowering of anti-hypertensive drugs [12].

The results of our study are in agreement with Hermida et al. who has also studied this phenomenon in patients with refractory hypertension [19, 23]. Nevertheless, our series has several different clinical characteristics. Our patients had more severe hypertension in terms of BP values: 142 versus 136 mmHg for mean SBP, amount of hypotensive medication: 4 versus 3 and non-dipper profile on ABP: 100 versus 79%. Moreover, their treatment strategy consisted in changing one drug from morning to bedtime; in the present study, we decided to move all the drugs to bedtime except the diuretic that was kept in the morning. Finally, an important difference from the Hermida et al. study was that they modified the treatment strategy by interchanging the third of the drugs, mainly a calcium channel blocker and an α-blocker, while in our study, we maintained exactly the same drugs at the same doses.

The usefulness of chronotherapy approach has also been recently proven in a study of 32 patients with chronic kidney disease and non-dipper BP on ABP but normal daytime ABP (<135/85 mmHg). After shifting one anti-hypertensive from the morning to evening, they observed an improvement in BP circadian rhythm and a decrease in proteinuria [22].

In our series, all the patients had RAH with non-dipper or riser profile. After chronotherapy, 15% of the patients moved from a non-dipper to a dipper profile. However, because of the limited statistical power available in the current study, this change was not statistically significant.

The main limitation of our study is the small sample size. In our clinical setting, most patients taking more than two anti-hypertensive drugs follow a schedule including intakes of pills at times other than in the morning. This fact and the high requirements in terms of BP values are the reasons why only a few patients met eligibility criteria.
Another potential limitation of this study is the lack of randomization, as it was designed as an observational prospective study with a control group. This facilitates possible bias related to the study design and the regression to the mean phenomenon. Although ideally a randomized design would have been used, it is of note to mention the great difficulty, for the independent clinician, to perform a randomized clinical trial due to the demanding economic expenditure required to cover insurance costs. In any case, the value of this kind of study has recently been highlighted [26, 27].

Our results and the increasing evidence, favouring the concept of chronotherapy, would suggest, especially when dealing with RAH, a clear indication for performing ABP as BP profile must be considered when deciding the timing of the anti-hypertensive medication. We believe it is time to consider applying chronotherapy concepts to clinical practice since this could contribute to improve BP control and the long-term prognosis of patients with RAH.

In conclusion, the present study shows that in patients with RAH and non-dipping profile, the shift of all antihypertensive drugs, with the exception of diuretics, from morning to evening is effective in partially restoring the normal circadian rhythm. This effect can be achieved, as our results show, without any change in the amount of administered anti-hypertensive drugs, suggesting that chronotherapy may play a role in the treatment of RAH. Further and larger studies will be needed to evaluate if the effectiveness of chronotherapy at decreasing BP translate in a reduction of cardiovascular morbidity and mortality.

Conflict of interest statement. None declared.

References

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