Circadian Blood Pressure Variation in Hypertensive Patients With Primary Hyperaldosteronism

George A. Mansoor, William B. White

Abstract—A less-than-normal decline in nocturnal blood pressure (BP) has been associated with excessive hypertensive complications. This is concerning because secondary hypertension is often associated with this so-called nondipper BP profile. A nondipping pattern is more frequently found in the presence of pheochromocytoma, Cushing’s syndrome, and sleep apnea syndrome, but the prevalence is unclear in patients with primary hyperaldosteronism. We therefore studied ambulatory BP profiles in 16 hypertensive patients with primary hyperaldosteronism and an equal number of essential hypertensive subjects. The awake–sleep BP difference of the hyperaldosteronism patients was similar to that of essential hypertensives (15/14±3/2 versus 14/9±3/2 mm Hg, P=NS). The prevalence of dippers and nondippers (according to two distinct criteria) in the two groups was similar. Repeat ambulatory BP monitoring in 12 subjects with primary hyperaldosteronism after specific intervention (3 after surgical removal of an adrenal adenoma and 9 after commencement and titration of spironolactone therapy) showed highly significant reductions in office BP (22/10±6/4 mm Hg, P<.05) and awake and sleep BP. However, the extent of nocturnal BP decline was unchanged between the two studies (17/16±3/3 versus 16/12±2/2 mm Hg, P=NS). There was no correlation between the awake–sleep difference and serum or urinary aldosterone levels or the aldosterone-to-renin ratio. In this study, we did not detect any differences in the awake–sleep differences between a group of hypertensives with primary hyperaldosteronism and a control group of essential hypertensives. (Hypertension. 1998;31:843-847.)

Key Words: blood pressure, ambulatory ■ hyperaldosteronism ■ blood pressure variability ■ hypertension, secondary

The circadian BP profile is likely a result of the complex interaction of neurological and hormonal circadian changes and the superimposed effects of physical and mental activity and posture.1,2 As part of this variation, there is a long-standing observation that BP decreases in the majority of normotensive and hypertensive subjects during sleep.3 Therefore, a terminology has come into practice for subjects with normal sleep BP decline who are labeled dippers and those with a less-than-expected decline are called nondippers. These categories are not clearly defined, and the extent of BP reduction during sleep is affected by several factors such as age, sleep quality, and underlying comorbidity.3,5 For example, autonomic failure,6 Shy-Drager syndromes,7 catecholamine excess states,8 chronic renal failure,9 Cushing’s syndrome,10 and diabetes mellitus11 are all associated with an attenuation of the nocturnal BP decline. However, there are conflicting reports8,12–17 on whether patients with primary hyperaldosteronism have a normal circadian BP profile.

The issue of whether the BP profile is altered in subjects with primary hyperaldosteronism is a relevant one because the nondipper profile is associated with excess hypertensive complications.18–22 We therefore have prospectively evaluated the circadian BP profiles of 16 subjects with newly diagnosed primary hyperaldosteronism and compared them with the profiles of 16 essential hypertensive control subjects. Furthermore, the effects of specific therapy (ie, surgical excision of an adenoma and aldosterone antagonists) on the circadian BP profiles have also been studied.

Methods

Patients and Control Subjects

The study protocol was approved by the Institutional Review Board and conducted according to its guidelines. The study patients and control subjects were all evaluated at our referral center for hypertension and vascular diseases. They were all referred by their physicians for evaluation of their hypertensive disease process because of its severity, the suspicion of secondary hypertension, or reports by the patient of multiple side effects from antihypertensive medications. Patients were evaluated for primary hyperaldosteronism if they developed spontaneous hypokalemia (serum K+ <3.6 mmol/L) or marked diuretic-induced hypokalemia (serum K+ ≤3.0 mmol/L) or had refractory hypertension. We studied 11 women and 5 men diagnosed with primary hyperaldosteronism as well as 16 subjects with essential hypertension. Five of these patients developed severe hypokalemia while taking diuretics, whereas 10 developed spontaneous hypokalemia and 1 subject was evaluated primarily because of resistant hypertension. Patients were diagnosed in a standard way with multiple measurements of serum and urinary aldosterone, plasma renin activity, and urinary potassium levels on a high sodium diet after hypokalemia had been corrected. Those patients with elevated urinary aldosterone levels, elevated serum aldosterone levels, or elevated aldosterone-renin

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ratios underwent computed axial tomography with sections at 2.5-mm intervals to exclude an adenoma. In some subjects, adrenal vein sampling (4 patients) and [131I]iodomethyl-19-norcholesterol (NP-59) adrenocortical scintigraphy with dexamethasone suppression (4 patients) were performed. There were 4 subjects diagnosed with an adrenal adenoma and 12 had bilateral adrenal hyperplasia.

Control subjects with essential hypertension were taken from our ambulatory BP monitoring database. These control subjects had been referred to us for similar reasons as the primary hyperaldosteronism patients but were found to have essential hypertension. Matching control subjects were within 5 years of age, of the same gender, and had office BP readings within 5 mm Hg.

Repeat Ambulatory BP Study

We repeated the ambulatory BP study in 3 subjects with aldosterone producing adenoma 3 months after surgery (on no antihypertensive therapy) and in 9 subjects with adrenal hyperplasia after 3 to 6 months of spironolactone therapy. Patients diagnosed as bilateral adrenal hyperplasia were treated with spironolactone in addition to the patients’ current antihypertensive therapy and then titrated upward to a minimum of 100 mg/d. If BP control was achieved, then withdrawal of other antihypertensives was attempted.

BP Measurements

Office BP was measured in standard fashion with the patient sitting for ≥5 minutes. The SBP was taken as the first sound on deflation of the cuff (Korotkoff phase I), and the DBP was taken as the complete disappearance of Korotkoff sounds (Korotkoff phase V). At least two readings were taken and averaged to give the office BP used in this analysis.

Twenty-four–hour ambulatory BP monitoring was performed on 9 subjects in each group using the Quiectril recorder (Welch Allen, Tyco) and on 7 subjects in each group with the Accutracker II monitor (Suntech Medical Instruments). All patients were studied on a typical workday, and none performed night shift work. The results of the BP monitor had to agree with the mercury sphygmomanometer within 5 mm Hg before the study was started. Readings were made every 15 minutes during the daytime (8:00 AM to 9:59 PM) and at least every 30 minutes at night (10:00 PM to 7:59 AM). The obtained data were manually entered into a computer and edited according to previously described criteria.23 All subjects kept a written diary of activities and actual sleep times, and this was used to separate the awake and sleep BP periods as well as for the awake—sleep BP difference (expressed as a percentage of awake BP and as an absolute value in mm Hg). The awake—sleep BP averages were also expressed as a ratio percentage.4 Demographic variables between the study patients and control subjects were tested by χ2 analysis or t tests as appropriate. Correlation coefficients were calculated by the Pearson method, and all values of P < .05 were considered significant. Changes in the paired BP data were analyzed in a standard way with paired t tests.

Results

Baseline Demographics

Demographic characteristics of the primary hyperaldosteronism patients and their control subjects are shown in Table 1. The two groups were matched for age, body mass index, treatment status, and office BPs. Eleven patients in the primary hyperaldosteronism group and 10 patients in the control group were receiving pharmacological therapy. In the secondary hypertension group, 2 patients were receiving three drugs, 4 patients were receiving two drugs, and 5 patients were receiving one drug. In the control group, 1 patient was receiving four drugs, 2 patients were receiving three drugs, and 7 patients were receiving one drug. One subject in each group had adult-onset diabetes mellitus at the time of the ambulatory BP study. No subject in either group had congestive heart failure, renal insufficiency (serum creatinine ≥133 μmol/L), or orthostatic hypotension and no patient in either group was receiving corticosteroids. The mean duration of hypertension before the diagnosis of primary hyperaldosteronism was 13 ±3 years (range, 1 to 40 years; median, 11 years). The hyperaldosteronism group, as expected, had low serum potassium levels (mean, 3.9 ± 0.3 mEq/L), elevated serum aldosterone of 655 ± 99 pmol/L (normal, 56 to 250 pmol/L), elevated urinary aldosterone of 75 ± 11 nmol/d (normal, <39 nmol/d), and elevated serum aldosterone-to-renin ratio of 130 ± 30 (aldosterone expressed in ng/dL and renin expressed in ng/mL per hour).

Statistical Analysis

All statistical analyses were performed using JMP (v3.0 statistical software for Macintosh (SAS Institute). Variables that were not normally distributed were log transformed before analyses. Data are shown as mean ± SEM unless otherwise stated. Descriptive statistics were calculated for the awake and sleep periods as well as for the awake—sleep BP difference (expressed as a percentage of awake BP and as an absolute value in mm Hg). The awake—sleep BP averages were also expressed as a ratio percentage.4

### Table 1. Clinical Characteristics of Two Groups of Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Hyperaldosteronism</th>
<th>Essential Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>F/M</td>
<td>11/5</td>
<td>11/5</td>
</tr>
<tr>
<td>Age, y</td>
<td>55 ± 3</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>Antihypertensive therapy, n</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 2</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>Office SBP/DBP, mm Hg</td>
<td>165/97 ± 5/3</td>
<td>163/100 ± 5/3</td>
</tr>
<tr>
<td>Awake SBP/DBP, mm Hg</td>
<td>154/90 ± 4/3</td>
<td>150/88 ± 4/3</td>
</tr>
<tr>
<td>Sleep SBP/DBP, mm Hg</td>
<td>139/76 ± 6/3</td>
<td>136/79 ± 6/3</td>
</tr>
<tr>
<td>Awake BP loads, %</td>
<td>64/44</td>
<td>69/46</td>
</tr>
<tr>
<td>Sleep BP loads, %</td>
<td>66/38</td>
<td>71/47</td>
</tr>
</tbody>
</table>

All comparisons are nonsignificant. Values are mean ± SEM.

*A load thresholds are 140/90 mm Hg while awake and 120/80 mm Hg during sleep. BP loads were calculated as the percentage of elevated measurements during a particular period.
patients with adenomas, the two subgroups were combined for analysis.

Clinic and Ambulatory BPs

The two groups were moderately hypertensive (stage 2) with >50% SBP loads but had similar clinic, 24-hour, awake, and asleep BP averages (Table 1). The awake–sleep differences in the hyperaldosteronism group and the essential hypertension group were also similar in the two groups (Table 2), whether expressed as an absolute value in mm Hg (15/14±3/2 versus 14/9±3/2 mm Hg) or as a sleep-to-awake ratio percentage (90/85±2/3% versus 90/90±2/3%). The mean percentage decline in sleep BP (awake–sleep BP difference/awake BP) was 13±2% in the study group and 10±2% in the control group (P=.05). There were 11 dippers in the study group and 8 dippers in the control group according to criterion A but 15 and 13, respectively, according to the criterion B. There were no differences between dippers and nondippers in regard to serum and urinary aldosterone levels and aldosterone-to-renin ratio (data not shown). There also were no differences in the nocturnal BP decline in patients with adenoma and those with bilateral adrenal hyperplasia (data not shown).

In the 12 patients in whom repeat ambulatory BP studies were performed, there was a highly significant decline in office and ambulatory BPs (Table 3), but the awake–sleep BP difference remained unchanged. The BP load declined significantly for both awake (70/50±9/9% versus 30/16±10/3%, P<.05) and sleep (68/40±10/10% versus 38/14%, P<.05) BP. The three patients with adenomas who had a repeat ambulatory BP study were all normotensive at the repeat study (24-hour BP, <135/85 mm Hg), and of the remaining 9 with bilateral adrenal hyperplasia, only 3 subjects had an average 24-hour BP of >135/85 mm Hg. No patient had 24-hour SBP of >160 mm Hg or 24-hour DBP of >90 mm Hg. The number of dippers at the first and second studies was 8 and 9, respectively, according to criterion A, and 11 and 11, respectively, according to criterion B.

Relationship of BP to Biochemical Values

There were no significant correlations between office or ambulatory BP and serum aldosterone, urinary aldosterone, or the aldosterone-to-renin ratio. There also were no relationships between the awake–sleep differences and these biochemical parameters.

Discussion

The main finding of this study was that the circadian BP variation in subjects with primary hyperaldosteronism is preserved compared with that of essential hypertensives. Of note, the hyperaldosteronism patients studied here composed a group mainly with bilateral adrenal hyperplasia and stage 2 hypertension and were otherwise clinically uncomplicated. Our study examined the nocturnal decline as an absolute number in mm Hg relative to the awake pressure, as a

### Table 2. Comparison of Awake—Sleep Difference in BP Between the Two Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Hyperaldosteronism</th>
<th>Essential Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake—sleep BP difference, mm Hg</td>
<td>15±3</td>
<td>14±3</td>
</tr>
<tr>
<td>SBP</td>
<td>14±2</td>
<td>9±2</td>
</tr>
<tr>
<td>DBP</td>
<td>14±3</td>
<td>10±3</td>
</tr>
<tr>
<td>Asleep-to-awake ratio, %</td>
<td>90±2</td>
<td>90±2</td>
</tr>
<tr>
<td>SBP</td>
<td>85±3</td>
<td>90±3</td>
</tr>
<tr>
<td>DBP</td>
<td>87±2</td>
<td>90±2</td>
</tr>
<tr>
<td>Dipper/nondipper, A</td>
<td>11/5</td>
<td>8/8</td>
</tr>
<tr>
<td>Dipper/nondipper, B</td>
<td>15/1</td>
<td>13/3</td>
</tr>
</tbody>
</table>

All comparisons are nonsignificant. Values are mean±SEM. A, Nondippers defined as <10% decline in both SBP and DBP; B, nondippers defined as ratio of >10% for both SBP and DBP.

### Table 3. Comparison of Office and Ambulatory BP Before and After Treatment for Primary Hyperaldosteronism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Final</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mm Hg</td>
<td>165±7</td>
<td>144±6</td>
<td>.006</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>100±3</td>
<td>90±3</td>
<td>.045</td>
</tr>
<tr>
<td>Awake SBP, mm Hg</td>
<td>156±6</td>
<td>130±6</td>
<td>.003</td>
</tr>
<tr>
<td>Awake DBP, mm Hg</td>
<td>93±4</td>
<td>78±3</td>
<td>.0001</td>
</tr>
<tr>
<td>Asleep SBP, mm Hg</td>
<td>140±7</td>
<td>115±6</td>
<td>.003</td>
</tr>
<tr>
<td>Asleep DBP, mm Hg</td>
<td>77±3</td>
<td>67±3</td>
<td>.015</td>
</tr>
<tr>
<td>Awake BP load SBP/DBP, %</td>
<td>70/50</td>
<td>30/16</td>
<td>.001/.003</td>
</tr>
<tr>
<td>Asleep BP load SBP/DBP, %</td>
<td>68/40</td>
<td>38/14</td>
<td>.015/.04</td>
</tr>
<tr>
<td>Awake—asleep SBP difference, mm Hg</td>
<td>17±3</td>
<td>16±2</td>
<td>NS</td>
</tr>
<tr>
<td>Awake—asleep DBP difference, mm Hg</td>
<td>16±3</td>
<td>12±2</td>
<td>NS</td>
</tr>
<tr>
<td>Awake—asleep SBP difference, %</td>
<td>11±2</td>
<td>12±2</td>
<td>NS</td>
</tr>
<tr>
<td>Awake—asleep DBP difference, %</td>
<td>17±3</td>
<td>14±3</td>
<td>NS</td>
</tr>
<tr>
<td>Dippers/non-dippers, A</td>
<td>8/4</td>
<td>9/3</td>
<td>NS</td>
</tr>
<tr>
<td>Dippers/non-dippers, B</td>
<td>11/1</td>
<td>11/1</td>
<td>NS</td>
</tr>
</tbody>
</table>

A and B are defined in Table 2. Values are mean±SEM.
percentage of awake BP, as a ratio of sleep to awake BP, and categorically as dipper and nondipper according to two definitions. When 12 patients underwent ambulatory BP monitoring 3 to 6 months after specific intervention for primary hyperaldosteronism, there was a highly significant reduction in office and ambulatory BP averages and BP loads but no change in the awake–sleep BP differences according to any definition.

The reduction in mean arterial pressure of 13% and 10% in the primary hyperaldosteronism and essential hypertension groups, respectively, is well within the values described in large studies that examined the BP decline during sleep. For example, in their study of 1042 subjects with untreated essential hypertension, Schillaci et al. showed that individuals in the age group of 50 to 59 years have an 11.2/14.4±7/8% decline in systolic and DBP. Similarly, the calculated sleep–to–awake ratios in a large group of subjects with essential hypertension are similar to our findings.

It is problematic to researchers that different definitions and methods are used to express the circadian BP variation. Therefore, in our study we were careful to use more than one method so deficiencies in a particular method would not jeopardize our results. For the categorization of dippers and nondippers, we used two definitions that have been studied in a large number of subjects. The first criterion (A) was taken from a prognostic study done in Italy, in which a nondipping profile was found to have a deleterious effect on cardiovascular events in women. The second criterion (B) is from the large international database of >7000 patients, which is the most comprehensive analysis of nocturnal BP to date.

Our results are consistent with previous results that in general show the circadian BP variation is preserved in patients with primary hyperaldosteronism (Table 4). Not included in this table are the results of two other studies, from which the absolute awake–sleep drop in BP could not be calculated. A review of publications in this area shows considerable differences in methodology used by authors to examine the circadian BP profile. The cosinor method has been used by a few authors but is very rigid and imposes unrealistic limitations on the data. Also, there is variability in the definition of awake and sleep periods and in the methods. We used patient diaries to separate the ambulatory BP data and then calculate the BP difference; this method has been shown to avoid misclassification of the dipping status.

Our study also illustrates that specific therapy for primary hyperaldosteronism of surgical removal of an adrenal adenoma or administration of spironolactone significantly reduces office, awake, and sleep BPs as well as BP loads but does not affect the awake–sleep difference. Such effects of specific therapy on sleep BP have not been reported previously. Almost all patients with bilateral adrenal hyperplasia achieved good BP control with the addition of spironolactone to their regimen.

The possible ways that secondary hypertension may affect the circadian BP include sympathetic nervous system activation, fluid retention, and increases in peripheral vascular resistance. A reduction in the activity of the sympathetic nervous system during sleep is thought to be a major factor contributing to the normal decline in sleep BP. Many causes of secondary hypertension, such as pheochromocytoma, hyperthyroidism, and sleep apnea, but not primary hyperaldosteronism, do indeed appear to elevate sleep BP, primarily through activation of the sympathetic nervous system.

Our inability to detect a relationship between either office or ambulatory BP levels and serum or urine aldosterone levels are similar to the findings of Blumenfeld et al. who found a relationship between mean arterial pressure and urinary aldosterone in subjects with adrenomas but not in patients with bilateral adrenal hyperplasia.

Our study has several limitations. Our data were obtained in a small sample size but indicated that the essential hypertensive control subjects tended to have smaller awake–sleep BP declines. A larger study would help confirm our findings. Our conclusions cannot be assumed to apply to patients with more severe levels of hypertension due to primary hyperaldosteronism or to subjects with only aldosterone-producing adenomas. Furthermore, it is not possible to be sure whether differences in drug therapy and levels of physical activity affected our results.

In conclusion, primary hyperaldosteronism is associated with a normal circadian BP variability, and the specific treatment of primary hyperaldosteronism leads to a highly significant decline in all BP parameters but does not alter the extent of the nocturnal BP variation. Additional studies of larger number of subjects with both aldosterone-producing adenoma and adrenal hyperplasia are warranted to exclude a small blunting in sleep BP.

**Acknowledgment**

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**References**


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