Nocturnal Blood Pressure Dipping in the Hypertension of Autonomic Failure

Luis E. Okamoto, Alfredo Gamboa, Cyndya Shibao, Bonnie K. Black, André Diedrich, Satish R. Raj, David Robertson, Italo Biaggioni

Abstract—Blood pressure (BP) normally decreases during the night. Absence of this phenomenon (nondipping) is associated with increased cardiovascular risk. Altered autonomic and endocrine circadian rhythms are suspected to play a role. Patients with peripheral autonomic failure offer a unique opportunity to study this phenomenon, because ≈50% develop supine hypertension despite very low autonomic function. The purpose of this study was to define the prevalence of dipping in these patients and to determine whether dipping is associated with less severe autonomic impairment or exaggerated nocturnal sodium excretion. We collected BP and urine from 8:00 PM to 8:00 AM in 41 peripheral autonomic failure patients with supine hypertension. Dipping (systolic BP fall ≥10% during 12 AM to 6 AM) occurred in 34% of patients, with an average decrease of −44±4 mm Hg at 4 AM. Systolic BP, averaged from 12 AM to 6 AM, decreased to normotensive levels in 50% (n=7) of dippers and 15% (n=7) of nondippers. There were no significant differences in the severity of autonomic failure, nocturnal diuresis, or natriuresis (0.18±0.01 in dippers versus 0.18±0.01 mEq/mg of creatinine in nondippers; P=0.522) between groups. At 8:00 AM, orthostatic hypotension was similar between groups (−84/−35±9/4 mm Hg in dippers versus −93/−39±6/3 mm Hg in nondippers; P=0.356 for systolic BP). In conclusion, dipping was observed in one third of patients with peripheral autonomic failure, so that a significant percentage of patients would not require treatment for supine hypertension. Dipping was not associated with increased nocturnal urinary sodium or volume excretion or less severe autonomic failure. Thus, mechanisms independent of autonomic pathways contribute to BP dipping in these patients. (Hypertension. 2009;53[part 2]:363-369.)

Key Words: dipping ▪ supine hypertension ▪ autonomic failure ▪ circadian rhythm ▪ autonomic nervous system ▪ natriuresis

Blood pressure (BP) normally follows a circadian pattern characterized by a decline of ≥10% in mean BP levels from day to night (dipping). This phenomenon results from exogenous patterns of activity, stress, and posture during the 24-hour period,1,2 as well as endogenous circadian rhythms in autonomic nervous and endocrine systems.3 Alterations in these intrinsic circadian rhythms can result in the absence of the nocturnal BP decline (nondipping). This altered pattern is commonly seen in patients with essential hypertension, several forms of secondary hypertension, and disorders of the autonomic nervous system. The clinical relevance of this phenomenon lies in the fact that nondipping has been associated with increased frequency of hypertensive target organ damage (brain, heart, and kidney), as well as cerebrovascular and cardiovascular events in hypertensive patients.4-7

The autonomic nervous system is the main suspect in mediating the intrinsic circadian variation in BP. In support of this, nondipping has been reported in autonomic failure (AF) patients.8,9 The underlying mechanism, however, is not clear, and it is not known whether alterations in circadian regulation of diuresis and natriuresis, known to be reversed in these patients,10 could contribute to the abnormal BP profile.

Primary AF can occur with central nervous system manifestations (multiple system atrophy) or with peripheral autonomic impairment (pure AF [PAF] and Parkinson’s disease [PD+]). Both are characterized by severe orthostatic hypotension and, in approximately half of patients, supine hypertension.11 Patients with peripheral forms of AF are of particular interest, because their supine hypertension is not attributed to residual sympathetic activity,12 and they have very low levels of plasma norepinephrine and plasma renin activity.11

In the present study, we took advantage of the unique characteristics of these patients to determine the proportion of patients who dipped during the night and to whether dipping is associated with less severe autonomic impairment or exaggerated nighttime urinary sodium or water excretion.
Methods

Subjects
We studied 41 patients with peripheral AF: 33 with PAF (21 men; 72±1 years of age; body mass index: 24.97±0.58 kg/m²) and 8 with PD (+ (4 men; 73±2 years of age; body mass index: 24.69±1.43 kg/m²). Patients were diagnosed following the criteria of the American Autonomic Society.13 All of the patients had supine hypertension as defined as supine systolic BP >150 mm Hg at 8 PM. Patients with secondary forms of AF (eg, diabetes mellitus or amyloidosis) were excluded. All of the studies were approved by our institutional review board, and written informed consent was obtained from each subject before study entry.

General Protocol
Patients were admitted to the General Clinical Research Center at Vanderbilt University Medical Center. Medications affecting the autonomic nervous system, BP, and blood volume were discontinued for ≥5 half-lives before admission. Patients were placed on a diet consisting of low monoamine, caffeine-free food containing 150 milliequivalents of sodium and 70 milliequivalents of potassium per day. Studies were conducted ≥2.5 hours after a meal. The screening consisted of a medical history, physical examination, 12-lead ECG, and laboratory assessments. Standardized autonomic function tests were performed to assess the severity of autonomic impairment, as described previously.14 BP and heart rate (HR) were obtained using an automated oscillometric sphygmomanometer (Dinamap, GE Medical Systems Information Technologies), finger photoplethysmography (Finometer, FMS, or Nexfin, BMEYE), and continuous ECG. Baseline data were digitized for power spectral analysis of HR variability in 22 patients (17 PAF and 5 PD). Plasma norepinephrine, plasma renin activity, and plasma aldosterone were determined in the morning after the patient remained in the supine position overnight and again after 30 minutes in the upright position (or as long as tolerated). Blood samples were collected from a heparin lock placed ≥30 minutes before the first blood draw.

Overnight Blood Pressure Monitoring
Patients were studied for 12 hours starting at 8 PM. Patients were instructed to remain supine throughout the night with the head of the bed elevated 10°. Fluid intake was restricted, and BP was measured at 2-hour intervals by an automated sphygmomanometer (Dinamap, GE Medical Systems Information Technologies). At 8 AM, BP and HR were determined after 1 minute in the upright position or as long as tolerated. Urine was collected for 12 hours, from 8 PM to 8 AM, for determination of volume, sodium, and creatinine.

Dipping Definition
Overnight BP monitoring was arbitrarily divided into 2 parts: a baseline period (“daytime”) from 8 PM to 10 PM and a sleeping period (“nighttime”) from 12 AM to 6 AM.15 Nondipping was defined as a fall in average sleeping systolic BP <10% from baseline.

Overnight Medication Trial With Nitroglycerin
To compare the magnitude of BP dipping to that achieved with pharmacological treatment for supine hypertension, a subset of 15 nondippers was randomized, in a single-blinded crossover fashion, to receive on separate days either transdermal nitroglycerin 0.1 mg/h (Nitro-Dur patch, Key Pharmaceuticals) or placebo patch placed at 8 PM and removed at 6 AM. Supine BP and HR were measured as described above.

Spectral Analysis
Beat-to-beat R-R intervals were digitized and analyzed to determine the power spectra in the low-frequency (0.04 to 0.15 Hz) and high-frequency (0.15 to 0.40 Hz) ranges, as described previously.16

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Dippers, 34% (n=14)</th>
<th>Nondippers, 66% (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SEM, y</td>
<td>70±2</td>
<td>72±2</td>
<td>0.526</td>
</tr>
<tr>
<td>Gender (male/female), n/n</td>
<td>7/7</td>
<td>19/9</td>
<td>0.300</td>
</tr>
<tr>
<td>Duration of disease, mean±SEM, y</td>
<td>5.9±0.9</td>
<td>7.7±1.1</td>
<td>0.536</td>
</tr>
<tr>
<td>PMH of HTN (n=8), % (n)</td>
<td>21 (3)</td>
<td>19 (5)</td>
<td>0.824</td>
</tr>
<tr>
<td>BMI, mean±SEM, kg/m²</td>
<td>24±1</td>
<td>25±1</td>
<td>0.350</td>
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<tr>
<td>Plasma creatinine, mean±SEM, mg/dL</td>
<td>1.06±0.05</td>
<td>1.21±0.08</td>
<td>0.454</td>
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<tr>
<td>BP (mm Hg) and HR (bpm) monitoring</td>
<td></td>
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<tr>
<td>8 PM to 10 PM (baseline), mean±SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>182±4</td>
<td>175±3</td>
<td>0.215</td>
</tr>
<tr>
<td>DBP</td>
<td>93±2</td>
<td>90±2</td>
<td>0.434</td>
</tr>
<tr>
<td>HR</td>
<td>71±2</td>
<td>67±1</td>
<td>0.106</td>
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<tr>
<td>12 AM to 6 AM (sleeping period), mean±SEM</td>
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<td></td>
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<tr>
<td>SBP</td>
<td>147±5</td>
<td>171±4</td>
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<tr>
<td>DBP</td>
<td>81±3</td>
<td>89±2</td>
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<tr>
<td>HR</td>
<td>68±2</td>
<td>65±1</td>
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<tr>
<td>8 AM, mean±SEM</td>
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<td></td>
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<tr>
<td>SBP</td>
<td>163±6</td>
<td>175±5</td>
<td>0.161</td>
</tr>
<tr>
<td>DBP</td>
<td>88±3</td>
<td>92±3</td>
<td>0.395</td>
</tr>
<tr>
<td>HR</td>
<td>72±3</td>
<td>68±2</td>
<td>0.152</td>
</tr>
<tr>
<td>Normalization of nighttime SBP, % (n)</td>
<td>50 (7)</td>
<td>15 (4)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

PMH indicates past medical history; HTN, essential hypertension; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP.

*Percentage of patients with a systolic BP averaged between 12 AM and 6 AM of <150 mm Hg.

Laboratory Measurements
Plasma norepinephrine levels were determined by high-performance liquid chromatography with electrochemical detection. Plasma renin enzymatic activity was assayed by the conversion of angiotensinogen to angiotensin I by radioimmunoassay. Serum aldosterone was measured by radioimmunoassay.

Statistical Methods
The main outcome variable was the mean systolic BP during the sleeping period. All of the values are presented as means±SEMs. Normal distribution of data was assessed by the Kolmogorov-Smirnov test. If data did not have a normal distribution, nonparametric statistical tests (Mann-Whitney U test for independent groups or Wilcoxon signed-rank test for 2 related groups) were used. Differences in mean BP and mean HR at baseline, sleeping period, and at 8 AM between dippers and nondippers were analyzed by unpaired t tests. Differences in BP and HR within each group were analyzed by paired t tests.

Comparisons between dippers and nondippers were analyzed by Student t tests if they had normal distribution. Otherwise, nonparametric tests were used. Pearson’s χ² test was used for nominal variables.

All of the tests were 2-tailed, and a P value of <0.05 was considered significant. Analyses were performed with SPSS 16.0 (SPSS Inc.).
Results

Baseline Characteristics and BP Monitoring

Patient characteristics are shown in Table 1. A dipper pattern was observed in 14 patients (34%; 10 PAF and 4 PD+) and a nondipper pattern in 27 patients (66%; 23 PAF and 4 PD+). There were no significant differences in age, gender distribution, duration of disease, history of essential hypertension, body mass index, or plasma creatinine between the 2 groups. Of the 41 patients with peripheral AF and supine hypertension, only 8 patients (20%) had a past medical history of essential hypertension: 3 dippers (21%) and 5 nondippers (19%).

The mean systolic BP at baseline (8 PM to 10 PM) was nonsignificantly higher in dippers (Table 1; P=0.215). By definition, mean systolic BP during the sleeping period was lower in dippers (P=0.001). The maximal decrease in systolic BP was −44 ± 4 mm Hg at 4 AM in dippers (from 182 ± 4 mm Hg at baseline to 138 ± 6 mm Hg; Figure 1), whereas nondippers decreased −8 ± 4 mm Hg (from 175 ± 3 mm Hg to 167 ± 5 mm Hg). Among dippers, 50% (n=7) decreased their mean systolic BP during the sleeping period to normotensive levels (systolic BP <150 mm Hg) compared with 15% (n=4) of nondippers (P=0.016). At 8 AM, the mean systolic BP was similar between groups (P=0.161), but dippers tended to have lower systolic BP values. The pattern of diastolic BP was similar to the systolic BP, with a significantly lower diastolic BP during the sleeping period in dippers (Figure 1; P=0.039); mean diastolic BP decreased from 93 ± 2 to 81 ± 3 mm Hg during the sleep period (P=0.001 by paired t test). Mean HR at baseline, sleeping period, and at 8:00 AM did not differ significantly between dippers and nondippers; however, dippers tended to have higher HR in all of the periods. There was a small but consistent decrease in HR during the sleeping period compared with baseline in dippers (71 ± 2 versus 68 ± 2 bpm; P=0.044 by paired t test). Nondippers had a similar pattern but did not reach statistical significance (67 ± 1 versus 65 ± 1 bpm; P=0.066 by paired t test).

At 8 AM, a similar proportion of dippers and nondippers were unable to stand up because of profound orthostatic symptoms (7% versus 11%, respectively). In the remaining patients, both groups had a similar profound decrease in systolic and diastolic BPs (−84 ± 35 ± 9/4 mm Hg in dippers versus −93/−39 ± 6/3 mm Hg in nondippers; P=0.356 for systolic BP and P=0.494 for diastolic BP) without an adequate increase in HR (10 ± 4 bpm in dippers versus 10 ± 2 bpm in nondippers; P=0.892; Figure 2).

Autonomic Testing, Power Spectral Densities, and Neurohormonal Determinations

The results of the autonomic testing, power spectral densities, and neurohormonal determinations are presented in Table 2. Supine BP was 164 ± 7/88 ± 4 and 170 ± 5/92 ± 3 mm Hg in dippers and nondippers, respectively (P=0.551 for systolic BP and P=0.388 for diastolic BP). Supine HR was 74 ± 3 and 68 ± 2 bpm in dippers and nondippers, respectively (P=0.075). With standing, both groups had a similar profound decrease in BP without an adequate increase in HR.Valsalva maneuver was performed in 39 patients, and all had a significant decrease in systolic BP during phase II, which was similar between the 2 groups. Phase IV BP overshoot (increase in systolic BP >10 mm Hg from baseline) was absent in all of the dipper patients, whereas it was present in 2 nondipper patients (both had PD+). These 2 patients had disabling orthostatic hypotension and had significant abnormalities in the remaining autonomic tests. Both dippers and
nondippers had markedly reduced sinus arrhythmia, Valsalva HR ratio, and BP response to pain stimulus (cold pressor test). There were no differences between groups.

Spectral analysis of HR variability was available in 22 patients, 10 dippers and 12 nondippers. Both had a markedly blunted high-frequency and low-frequency components compared with normal controls (Table 2), and there were no differences between groups. Normalized units for the high-frequency and low-frequency components compared with normal controls (Table 2), and there were no significant differences between supine and upright plasma aldosterone levels between the 2 groups.

**Nocturnal Urinary Volume and Sodium Excretion**

Complete nighttime urine collections were obtained in 35 patients: 11 dippers and 24 nondippers. Nighttime urinary volume did not differ significantly between dippers and nondippers (979±133 mL versus 1097±99 mL, respectively; \(P=0.644\); Figure 3). Likewise, urinary sodium excretion was similar between the 2 groups (0.184±0.01 mEq/mg of creatinine in dippers versus 0.177±0.01 mEq/mg of creatinine in nondippers; \(P=0.522\)).

**Overnight BP Reduction With Dipping and Nitroglycerin**

Average supine systolic BP at baseline was similar in dippers and nondippers receiving placebo or nitroglycerin (182±4, 179±5, and 171±5 mm Hg, respectively). The mean decrease in systolic BP at 4 AM (maximal decrease) was significantly greater in dippers compared with nondippers receiving nitroglycerin or placebo (−46±5 versus −24±6 and −7±4 mm Hg, respectively; \(P<0.01\); Figure 4).
Discussion

BP fluctuates with a pattern that follows a circadian rhythm, with a peak in the early morning hours, and a trough during sleep. Circadian rhythms typically originate in “master oscillators” located in the suprachiasmatic nuclei of the anterior hypothalamus. How this hypothalamic rhythm is translated into changes in BP is not entirely known, but the autonomic nervous system is suspected to play a role; sympathetic activity is also modulated by hypothalamic centers and follows a circadian pattern similar to that of BP.

Absence of this circadian rhythm in BP (“nondipping”) is more commonly seen in hypertensive subjects and is a risk factor for the development of end-organ damage and poor cardiovascular outcomes. It has been proposed that nondipping in hypertensive patients is associated with an increase in sympathetic activity or a failure of sympathetic activity to decrease during the night.

Here we report that patients with PAF have a very high prevalence (66%) of nondipping, although they are characterized by very low and fixed sympathetic activity. These results demonstrate that increased sympathetic tone is not essential in the pathogenesis of the nondipping phenomenon and suggest that a more important determinant is the failure to modulate sympathetic activity.

Reversal of the normal circadian BP pattern has been reported previously in AF. It is not, therefore, unexpected that we found a high incidence of nondipping in our patients. The other side of this coin, and perhaps a more interesting finding of this study, is that BP spontaneously decreased during the night (dipping) in one third of the patients with severe peripheral AF and supine hypertension; 34% of our patients had a nocturnal fall in BP, with a decrease in systolic BP of \( \sim 44 \pm 4 \) mm Hg at 4 AM.

It should be noted that the classic definition of dipping, which is based on the average BPs during daytime and nighttime hours, cannot be readily applied to our patients. Patients with AF are very sensitive to stimuli that would normally produce little, if any, effect in BP. For example, upright posture lowered systolic BP by \( \sim 90 \) mm Hg in our patients. Meals have a similar dramatic hypotensive effect, whereas water drinking can produce substantial increases in BP. Daytime BP, therefore, is extremely variable because of seemingly trivial external factors that are difficult to control. Hence, it is difficult to rely on standard 24-hour BP monitoring to determine whether an intrinsic circadian pattern of BP is still present in these patients. Previous studies have highlighted the fact that an abnormal 24-hour BP pattern in AF could be attributable simply to the fact that orthostatic hypotension will lower the average daytime BP. Even when daytime activities were carefully controlled, postprandial hypotension confounded the BP measured during the scheduled supine periods.

This constraint required us to define the “daytime” (baseline) period from 8 PM to 10 PM and the “nighttime” (sleeping) period from 12 AM to 6 AM. The latter approach has been shown to provide an accurate estimate of BP during sleep, whereas wider intervals may overestimate the true sleeping BP. Future studies would benefit from careful 24-hour monitoring in these patients, to include periods of supine rest at intervals during the day, with strict control of physical activities, meals, water ingestion, and other confounding factors. This would test the validity of our ad hoc definition of dipping. Nonetheless, the clear separation in BP between our dipping and nondipping groups supports the adequacy of our definition. Furthermore, careful examination of individual data from previous studies shows that, in some of those patients, BP peaked early in the evening and decreased thereafter. This dipping phenomenon was indeed recognized previously by some investigators but has not been systematically studied before. Thus, despite differences in the precise definition of dipping, it is clear that this phenomenon is present in a significant minority of AF patients.

The mechanism underlying this BP dipping was not apparent from our studies, but our results showed that it was not because of less severe autonomic impairment and was not associated with increased urinary sodium or volume excretion during the night. It is unlikely that dipping in our patients was related to residual sympathetic tone, because we studied patients with extreme cases of peripheral sympathetic and parasympathetic impairment known to have very low residual sympathetic activity. Furthermore, there were no significant
differences in the severity of the autonomic impairment between dippers and nondippers (Table 2). Also, both groups of patients had very low levels of plasma renin activity, consistent with previous findings showing low and unresponsive plasma renin activity in PAF patients.25 In contrast, central regulatory pathways are intact in these patients, as evidenced by their preserved baroreflex-mediated release of vasopressin.26 It is possible, therefore, that release of vasoactive hormones, following a conserved circadian pattern, could have explained their BP dipping. This hypothesis, however, remains to be tested.

AF patients have a reversal of the diurnal variation in urinary output, with urinary volumes typically twice as large during the night as during the day.10,27 Supine hypertension is thought to contribute to this phenomenon by inducing pressure natriuresis. Because AF patients are extremely sensitive to changes in plasma volume,28 we speculated that dippers would have a greater diuresis as the underlying cause for their fall in BP. This hypothesis proved to be incorrect, because we found no significant difference in nocturnal urinary sodium or water excretion between dippers and nondippers. Furthermore, we would have expected a sustained fall in BP throughout the night if volume loss was the determinant of dipping. Instead, we observed a restoration of BP at the end of the nighttime period, following a circadian pattern.

Although the mechanism of dipping is not apparent from our results, our findings have implications for the treatment of these patients. Patients with PAF have a relatively good survival prognosis, but the presence of supine hypertension has been associated with end-organ damage, such as ventricular hypertrophy.20 It is justifiable, therefore, to treat hypertension in these patients. Nitroglycerin patch, applied at bedtime and removed in the morning, is an effective agent to control supine hypertension.10,11,30 Unfortunately, nitroglycerin does not decrease nighttime diuresis and, therefore, does not improve orthostatic intolerance in the morning. Furthermore, treatment of supine hypertension is not without risks. In particular, pharmacological treatment of supine hypertension could potentially aggravate orthostatic hypotension during the night, increasing the risk of falls in patients. Treatment of supine hypertension, therefore, should only be directed to patients who would benefit the most. On the other hand, we found that 27% of all of our patients spontaneously normalized their BP during the night, and the magnitude of this BP reduction was even higher than that achieved with nitroglycerin in nondippers. This suggests that the decision for the treatment of supine hypertension should be based on overnight BP monitoring rather than a single daytime measure. Antihypertensive treatment in this setting could be not only unnecessary but potentially harmful to these patients.

Perspectives
Circadian variation in sympathetic tone is likely to be important in the genesis of normal BP dipping, but our results suggest that it is not essential, because it was observed in patients with the severest form of AF. Other factors, not yet discovered, are likely to contribute to normal dipping. Patients with AF offer a unique opportunity to explore these potential mechanisms further, given that these hemodynamic effects are magnified in these patients because of the extreme sensitivity they have to any pressor or depressor stimuli. Our results also highlight the importance of individualizing treatment in these patients; notably, BP normalized in a significant percentage of our patients with severe supine hypertension, precluding the need to treat this aspect of their disease.

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Disclosures
None.

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