Adrenergic, Metabolic, and Reflex Abnormalities in Reverse and Extreme Dipper Hypertensives

Guido Grassi, Gino Seravalle, Fosca Quarti-Trevano, Raffaella Dell’Oro, Michele Bombelli, Cesare Cuspidi, Rita Facchetti, Gianbattista Bolla, Giuseppe Mancia

Abstract—Limited information is available on whether and to what extent the different patterns of the nocturnal blood pressure profile reported in hypertension are characterized by differences in sympathetic drive that may relate to, and account for, the different day-night blood pressure changes. In 34 untreated middle-aged essential hypertensive dippers, 17 extreme dippers, 18 nondippers, and 10 reverse dippers, we assessed muscle sympathetic nerve traffic, heart rate, and beat-to-beat arterial blood pressure at rest and during baroreceptor deactivation and stimulation. Measurements were also performed in 17 age-matched dipper normotensives. All patients displayed reproducible blood pressure patterns at 2 different monitoring sessions. The 4 hypertensive groups did not differ by gender or 24-hour or daytime blood pressure. Muscle sympathetic nerve traffic was significantly higher in nondipper, dipper, and extreme dipper hypertensives than in normotensive controls (58.6±1.8, 55.6±0.9, and 53.3±0.8 versus 43.5±1.4 bursts/100 heartbeats, respectively; \(P<0.01\) for all), a further significant increase being detected in reverse dippers (76.8±3.1 bursts/100 heartbeats; \(P<0.05\)). Compared with normotensives, baroreflex–heart rate control was similarly impaired in all the 4 hypertensive states, whereas baroreflex-sympathetic control was preserved. The day-night blood pressure difference correlated inversely with sympathetic nerve traffic \((r=-0.76; \ P<0.0001)\) and homeostasis model assessment index \((r=-0.32; \ P<0.005)\). Thus, the reverse dipping state is characterized by a sympathetic activation greater for magnitude than that seen in the other conditions displaying abnormalities in nighttime blood pressure pattern. The present data suggest that in hypertension, sympathetic activation represents a mechanism potentially responsible for the day-night blood pressure difference. (Hypertension. 2008;52:925-931.)

Key Words: reverse dipping ■ extreme dipping ■ ambulatory blood pressure ■ sympathetic activity ■ baroreflex ■ hypertension

Use of ambulatory blood pressure (BP) monitoring allowed identification of 4 different patterns of the nocturnal BP profile (ie, the dipping, nondipping, extreme dipping, and reverse dipping type), each with a prevalence that makes it a rather common phenomenon to be seen in clinical practice.\(^1\)\(^\text{--}^3\) It also has been shown that these different BP patterns are associated with different rates of target organ damage and clinical outcome.\(^2\)\(^\text{--}^\text{12}\) However, information is limited and contradictory on whether individuals with these different BP patterns display differences in the factors involved in cardiovascular control that may relate to and account for the different day-night BP changes.\(^1\)\(^3\)\(^\text{--}^\text{18}\) This is particularly the case for a fundamental mechanism participating in day and night cardiovascular modulation such as the adrenergic nervous system.\(^1\)\(^9\)

The present study was aimed at addressing the above issue by using direct measurement of muscle sympathetic nerve activity (MSNA) via microneurography in untreated hypertensive patients whose belonging to the dipping, nondipping, extreme dipping, and reverse dipping pattern was confirmed by repeated ambulatory BP monitorings. Microneurographic measurements were coupled with assessment of baroreflex function and insulin sensitivity to determine the relative contribution of reflex and metabolic alterations to the sympathetic abnormalities.

Methods

Population

Our study was performed from a population of males and females referred to the outpatient cardiovascular risk and hypertension clinic of our Hospital (San Gerardo, Monza). Inclusion criteria were: (1) an elevated office (>140/90 mm Hg) and 24-hour (>125/79 mm Hg) BP; (2) no obesity (body mass index ≤30 kg/m\(^2\)); (3) no history of smoking, excessive alcohol consumption, and major cardiovascular or noncardiovascular disease, including diabetes mellitus; (4) no use of antihypertensive and other cardiovascular or metabolic drugs; (5) no echocardiographic evidence of left ventricular hypertrophy, alteration in renal function, or ultrasonographic evidence of carotid artery thickening or plaques; (6) no evidence of disease or conditions responsible for secondary hypertension; (7) no history, symptoms, or
clinical evidence of the sleep apnea syndrome based on the information collected throughout the Berlin Questionnaire, which has been shown to provide a sensitive, specific, and accurate evaluation of the presence/absence of this condition; (8) no history of regular exercise habit or involvement in physical training programs; (9) a cardiac sinus rhythm; and (10) no substantial difference (≤5.0 mm Hg systolic BP) between sitting and standing BP. In each subject, BP was measured 3 times in the sitting position using a mercury sphygmomanometer and taking the first and fifth Korotkoff sound to identify systolic and diastolic values, respectively. Ambulatory BP was obtained over the 24 hours using an oscillometric device (Spacelabs 90207; Spacelabs) and setting the readings at 15- and 20-minute intervals during the daytime (from 7 AM to 11 PM) and nighttime (from 11 PM to 7 AM) periods, respectively. The device was applied in the morning, and subjects were allowed to return home with the instruction to attend their usual activities and to come back to the hospital the following day for device removal. To minimize the problem of the limited reproducibility of the day and night BP profile, a second ambulatory BP monitoring was performed within a 2-week period. Based on the 2 ambulatory BP monitoring data, the hypertensive subjects were subdivided into 4 groups (ie, those who, compared with average daytime BP values, displayed a reduction in average nighttime systolic and diastolic BP >10% and <20%, >20% [extreme dippers, n=17], <10% [nondippers, n=18], or with no reduction at all or an increase in nocturnal BP [reverse dippers, n=10]). A group of age-matched subjects (n=17) with normal office (<140/90 mm Hg) and 24-hour (<125/79 mm Hg) BP was taken as control. The cutoff BP values for ambulatory normality or elevation were those mentioned by international guidelines. No patient reported, in the diary given at the time of the ambulatory BP monitoring sessions, alterations in the sleep quantity/quality during the procedure. The study protocol was approved by the ethics committees of the institutions involved. All of the subjects agreed to participate after being informed of the nature and purpose of the study.

Measurements

Sympathetic Nerve Traffic

Multiunit recording of MSNA was obtained from a microelectrode inserted in a peroneal nerve posterior to the fibular head, as reported previously. Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A; Tektronix), and recorded with BP and heart rate on an ink polygraph. The muscle nature of MSNA was established according to criteria described in previous studies, and recording was accepted only if the signal/noise ratio was >3. Under baseline conditions, MSNA was quantified as bursts incidence over time (bursts for minute) and bursts incidence corrected for heart rate values (bursts per 100 heartbeats). This quantification has been shown to provide reproducible values that differ only by 3.8% when assessed twice in the same session by a single investigator.

Baroreflex modulation of MSNA and heart rate was assessed via the vasoactive drug infusion technique. Briefly, phenylephrine was incrementally infused in an antecubital vein at doses of 0.4, 0.7, and 1.0 µg/kg-1 per minute and nitroprusside at doses of 0.4, 0.7, and 1.0 µg/kg-1 per minute. Each step was maintained for 5 minutes, and the drug initially infused was selected randomly. Mean BP (diastolic-one-third pulse pressure), MSNA, and heart rate were averaged for the 20 minutes before the infusion and the 5-minute period of each step infusion. Baroreceptor modulation of MSNA and heart rate was estimated by calculating the percentage of change in MSNA (integrated activity [ie, bursts per minute × mean bursts amplitude], expressed in arbitrary units) and the absolute change in heart rate in relation to the change in mean BP induced by each dose of the vasoactive drugs. In each patient, the ratio between MSNA or heart rate changes was analyzed separately for the 3-step infusions of phenylephrine and nitroprusside. Data were then further averaged to obtain MSNA- or heart rate–baroreflex sensitivity gain.

Other Measurements

Waist circumference was measured in centimeters, and body mass index was obtained by dividing body weight by the square of the height in meters. Plasma norepinephrine was measured by high performance liquid chromatography from a venous blood sample, which was used also to assess plasma glucose and insulin levels. The homeostasis model assessment (HOMA) index was obtained according to the following formula: fasting glucose × fasting plasma insulin/22.5, whereas total cholesterol, HDL cholesterol, serum creatinine, and creatinine clearance were assessed by standard methods. During the sympathetic nerve traffic recording and baroreflex testing, BP was monitored by a finger photoplethysmographic device (Finapres 2300; Ohmeda) capable of providing accurate beat-to-beat systolic and diastolic values.

Heart rate was monitored during the experimental session beat-to-beat by a cardiotachometer triggered by the R wave of an EKG lead. During the 24-hour ambulatory BP monitoring period, it was also calculated as day and night average values.

Protocol and Data Analysis

Sympathetic nerve traffic measurements were performed in the morning after overnight fasting. With the subject supine, the blood sample for plasma norepinephrine, plasma insulin, and plasma glucose determination was withdrawn. After a 30-minute interval, BP, heart rate, and MSNA were continuously measured during: (1) an initial 20-minute baseline period; (2) the intravenous infusion of one vasoactive drug; (3) a 30-minute recovery period followed by a second 20-minute baseline period; and (4) the infusion of the second vasoactive drug. Data were analyzed by a single investigator unaware of the study design and of the belonging of the patient to the different groups. Individual values recorded in the baseline state or during baroreceptor manipulation were averaged for each group and expressed as mean±SEM. Comparisons between groups were made by 2-way ANOVA and Bonferroni correction for multiple comparisons. The Pearson correlation coefficient was used to determine the relationship among MSNA, 24-hour BP, body mass index, HOMA index, plasma insulin, total cholesterol, HDL cholesterol, serum creatinine and creatinine clearance, baroreflex sensitivity, and day-night systolic and diastolic BP differences. To determine the factors more likely to be involved in the day-night BP difference, a multivariate analysis was performed using MSNA, 24-hour BP, body mass index, HOMA index, plasma insulin, total cholesterol, HDL cholesterol, serum creatinine and creatinine clearance, and baroreflex sensitivity as the independent variables. P<0.05 was taken as the minimal level of statistical significance.

Results

As shown in the Table, the different groups of subjects had a similar age and gender distribution. Clinic and 24-hour systolic and diastolic BP values were significantly higher in the 4 hypertensive groups compared with the normotensive control one but almost superimposable in dipper, nondipper, extreme dipper, and reverse dipper hypertensives. Twenty-four-hour mean heart rate values were not significantly different in the normotensive and hypertensive groups, which also showed a similar day-night heart rate fall except for the reverse BP dipper hypertensive group, in which nocturnal bradycardia was significantly attenuated. All patients belonged to the category of the lower risk of obstructive sleep apnea of the Berlin questionnaire, reporting no symptoms of...
snoring and no evidence of waketime sleepiness, drowsy driving, or both.

Resting MSNA and Dipping Pattern

Resting MSNA data are shown in Figure 1. Both when expressed as bursts incidence over time and bursts incidence corrected for heart rate, MSNA was markedly and significantly greater in all 4 groups of hypertensive patients than in the normotensive group. The increase was not significantly different in dipper, nondipper, and extreme dipper hypertensives but greater in the reverse dipper hypertensive group (+76.4%; \( P<0.05 \)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT (n=17)</th>
<th>DHT (n=34)</th>
<th>NDHT (n=18)</th>
<th>EDHT (n=17)</th>
<th>RDHT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46.9±2.3</td>
<td>47.5±2.0</td>
<td>46.8±2.4</td>
<td>47.7±2.7</td>
<td>48.9±2.8</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/4</td>
<td>27/7</td>
<td>14/4</td>
<td>12/5</td>
<td>8/2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3±0.3</td>
<td>26.1±0.3</td>
<td>25.8±0.3</td>
<td>26.4±0.5</td>
<td>27.9±0.6</td>
</tr>
<tr>
<td>WC, cm</td>
<td>93.9±2.4</td>
<td>97.3±2.4</td>
<td>97.9±2.6</td>
<td>97.5±2.7</td>
<td>98.1±3.2</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>121.6±2.9</td>
<td>161.1±2.6*</td>
<td>162.7±2.9*</td>
<td>158.4±2.8*</td>
<td>164.9±3.2*</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>79.4±2.2</td>
<td>97.5±2.1*</td>
<td>98.8±2.5*</td>
<td>96.1±2.5*</td>
<td>99.8±2.7*</td>
</tr>
<tr>
<td>Clinic HR, bpm</td>
<td>69.4±2.0</td>
<td>73.6±1.9</td>
<td>72.5±2.8</td>
<td>73.1±2.6</td>
<td>73.8±2.8</td>
</tr>
<tr>
<td>24-Hour SBP, mm Hg</td>
<td>117.8±2.1</td>
<td>140.7±2.4*</td>
<td>142.5±2.3*</td>
<td>139.1±2.2*</td>
<td>143.8±2.8*</td>
</tr>
<tr>
<td>24-Hour DBP, mm Hg</td>
<td>73.2±1.9</td>
<td>85.4±1.6*</td>
<td>86.8±2.0*</td>
<td>87.5±2.2*</td>
<td>87.2±2.3*</td>
</tr>
<tr>
<td>24-Hour HR, bpm</td>
<td>67.5±2.2</td>
<td>70.8±1.6</td>
<td>70.6±2.4</td>
<td>71.8±2.3</td>
<td>72.2±2.9</td>
</tr>
<tr>
<td>Day-night SBP, %</td>
<td>-17.1±0.4</td>
<td>-14.7±0.3</td>
<td>-7.7±0.4*</td>
<td>-27.9±1.9†</td>
<td>0.7±0.4*</td>
</tr>
<tr>
<td>Day-night DBP, %</td>
<td>-18.3±0.3</td>
<td>-16.6±0.3</td>
<td>-8.2±0.3*</td>
<td>-25.1±0.7</td>
<td>2.5±0.7*</td>
</tr>
<tr>
<td>Day-night HR, bpm</td>
<td>-8.2±0.9</td>
<td>-9.7±0.6</td>
<td>-7.8±0.8</td>
<td>-10.2±1.1</td>
<td>-5.7±0.8†</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.8±0.5</td>
<td>5.1±0.5</td>
<td>5.3±0.6</td>
<td>5.2±0.6</td>
<td>5.5±0.7</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL</td>
<td>7.4±0.7</td>
<td>9.1±0.5</td>
<td>9.3±0.6</td>
<td>9.0±0.7</td>
<td>9.9±0.8</td>
</tr>
<tr>
<td>HOMA index, a.u.</td>
<td>1.59±0.2</td>
<td>2.11±0.2</td>
<td>2.25±0.3†</td>
<td>2.09±0.3</td>
<td>2.47±0.4†</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.91±0.03</td>
<td>0.95±0.01</td>
<td>0.96±0.03</td>
<td>0.94±0.02</td>
<td>0.95±0.03</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>96.2±5.1</td>
<td>97.3±4.5</td>
<td>98.1±5.5</td>
<td>95.8±5.6</td>
<td>97.8±6.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>202.2±4.5</td>
<td>210.5±4.3</td>
<td>211.7±4.8</td>
<td>209.4±5.0</td>
<td>213.2±6.1</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>56.5±1.1</td>
<td>54.3±0.9</td>
<td>54.7±1.1</td>
<td>54.5±1.7</td>
<td>54.6±1.4</td>
</tr>
<tr>
<td>Plasma NE, pg/mL</td>
<td>196.5±21</td>
<td>194.8±23</td>
<td>223.1±25</td>
<td>231.7±28</td>
<td>244.6±34</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>30.5±1.2</td>
<td>41.8±0.8†</td>
<td>44.6±1.4*</td>
<td>40.2±0.7†</td>
<td>56.8±2.4‡</td>
</tr>
<tr>
<td>MSNA, bursts/100 hb</td>
<td>43.5±1.4</td>
<td>55.6±0.9†</td>
<td>58.6±1.8*</td>
<td>53.3±0.8†</td>
<td>76.8±3.1‡</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; WC, waist circumference; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; NE, norepinephrine; hb, heartbeats; a.u., arbitrary units.

Data are shown as mean±SEM. *\( P<0.01 \); †\( P<0.05 \) vs NT; ‡\( P<0.05 \) vs DHT, NDHT, and EDHT.

Figure 1. Individual and mean (±SEM) resting MSNA values, expressed as bursts incidence over time (bs/min) and as bursts incidence corrected for heart rate (bs/100 heartbeats), in dipper normotensives (DNT) and in dipper (DHT), nondipper (NDT), extreme dipper (EDT), and reverse dipper (RDHT) hypertensives. *\( P<0.05 \); **\( P<0.01 \) vs DNT; †\( P<0.05 \) vs dipper hypertensives (DHT), nondipper hypertensives (NDHT), and extreme dipper hypertensives (EDHT).
Baroreflex Responses
As illustrated in Figure 2 (left panels), the 3 incremental doses of phenylephrine triggered a progressive increase in mean BP, which was accompanied by a progressive reduction in heart rate and in MSNA, whereas the 3 incremental doses of nitroprusside had opposite effects. The magnitude of the changes in MSNA induced by phenylephrine or nitroprusside was superimposable in the normotensive and the 4 hypertensive groups, which thus displayed similar values of the sensitivity of the baroreceptor–MSNA reflex (Figure 2, bottom right). In contrast, compared with the normotensive group, the concomitant heart rate changes and baroreflex–heart rate sensitivities were significantly and similarly smaller in the 4 hypertensive groups (Figure 2, top right).

Correlations
In the hypertensive population, there was a close inverse significant relationship between the resting MSNA values and the day-night BP differences (ie, the greater the sympathetic activation, the lesser the magnitude of the nocturnal hypotension; Figure 3). The day-night systolic and diastolic BP difference also correlated inversely with the HOMA index \( (r=-0.32 \text{ and } r=-0.29; P<0.005) \) and plasma insulin levels \( (r=-0.21 \text{ and } r=-0.23; P<0.05) \), whereas it showed no significant correlation with body mass index \( (r=0.17 \text{ and } r=0.12; P=NS) \), serum total cholesterol \( (r=-0.10 \text{ and } r=-0.09; P=NS) \), HDL cholesterol \( (r=-0.03 \text{ and } r=-0.06; P=NS) \), serum creatinine \( (r=0.07 \text{ and } r=0.05; P=NS) \), creatinine clearance \( (r=0.10 \text{ and } r=0.12; P=NS) \), 24-hour systolic and diastolic BP \( (r=-0.16, r=-0.11 \text{ and } r=-0.18 \text{ and } r=-0.15; P=NS) \), and baroreflex sensitivity \( (r=-0.006 \text{ and } r=-0.005; P=NS) \). Finally, in the hypertensive population of the study, resting MSNA levels did not show any significant correlation with either baroreflex–MSNA control or body mass index \( (r=0.18 \text{ and } r=0.16; P=NS \text{ for both}) \).

Discussion
The present study provides 2 novel pieces of information. First, it offers the first evidence that the reverse dipping BP pattern (ie, the condition characterized by no reduction or an increase in nighttime BP from the daytime values)\(^5,12,25\) is associated with a sympathetic activity that is greater than that characterizing individuals in whom BP shows a greater or smaller nighttime fall. Second, it shows, again for the first time, that in hypertension, there is a close inverse association between the degree of sympathetic activation and the magnitude of the nighttime fall in systolic or diastolic BP. That is, in individuals with a BP elevation, a greater sympathetic activation is accompanied by a reduced chance for BP to decrease at night, the most marked sympathetic activation leading to no nocturnal BP fall at all. Mechanistically, this might be accounted for by the fact that the sympathetic inactivation that takes place during sleep (and represents the major factor responsible for the sleep-related hypotension\(^12\)) is made progressively more difficult when, as it occurs in...
hypothesis, a variety of central and reflex influences converge to progressively increase sympathetic drive. On a clinical ground, this may suggest that the increased prevalence of organ damage and incidence of cardiovascular morbidity and fatal events described in conditions for which our patients did not provide any evidence of this involves not in line with the results of the Berlin questionnaire, which could depend, at least in part, on an increased prevalence of greater sympathetic activation seen in the reverse dippers. Two, the reverse BP dipping pattern was accompanied by nocturnal bradycardia, which was markedly less pronounced (-30.1%) than that observed in normotensive subjects, as well as in hypertensive subjects with different patterns of nocturnal BP fall. This may also be accounted for by a reduced ability of sympathetic activity to decrease at night because nighttime bradycardia has been shown to depend not only on a sleep-related increase in vagal tone but also on a sleep-related reduction in cardiac sympathetic drive.19,32 However, also in this case, the baroreflex does not appear to play a significant role because the baroreflex ability to modulate heart rate was similarly impaired in all hypertensive groups regardless of the greater or lower nocturnal BP reduction. Finally, our study encompasses some potential limitations. First, sleep quality and quantity during the 24-hour ambulatory BP monitoring could have affected the classification of the dipping status of our patients. However, the lack in each patient’s diary of any report of sleep alterations during the procedure does not support this hypothesis. Second, the greater sympathetic activation seen in the reverse dippers could depend, at least in part, on an increased prevalence of sleep apnea in these patients. However, this hypothesis appears not in line with the results of the Berlin questionnaire, for which our patients did not provide any evidence of this.
condition. Finally, the sympathetic activation we observed in patients with a reverse dipping profile may be not a phenomenon common to all clinical conditions characterized by such BP abnormality. Indeed, in patients with autonomic failure who frequently display a reverse dipping pattern, a reduction rather than an increase in sympathetic tone has been reported to take place.43

**Perspectives**

Our study has a clinical implication: that in the reverse dipping status, antihypertensive treatment may benefit from the inclusion of drugs capable of favorably interfering with sympathetic and metabolic abnormalities. This could improve nighttime BP control and reduce the elevated cardiovascular risk characterizing this hypertensive population.

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**Disclosures**

None.

**References**


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