Stroke Prognosis and Abnormal Nocturnal Blood Pressure Falls in Older Hypertensives

Kazuomi Kario, Thomas G. Pickering, Takefumi Matsuo, Satoshi Hoshide, Joseph E. Schwartz, Kazuyuki Shimada

Abstract—It remains uncertain whether abnormal dipping patterns of nocturnal blood pressure influence the prognosis for stroke. We studied stroke events in 575 older Japanese patients with sustained hypertension determined by ambulatory blood pressure monitoring (without medication). They were subclassified by their nocturnal systolic blood pressure fall (97 extreme-dippers, with ≥20% nocturnal systolic blood pressure fall; 230 dippers, with ≥10% but <20% fall; 185 nondippers, with ≥0% but <10% fall; and 63 reverse-dippers, with <0% fall) and were followed prospectively for an average duration of 41 months. Baseline brain magnetic resonance imaging (MRI) disclosed that the percentages with multiple silent cerebral infarct were 53% in extreme-dippers, 29% in dippers, 41% in nondippers, and 49% in reverse-dippers. There was a J-shaped relationship between dipping status and stroke incidence (extreme-dippers, 12%; dippers, 6.1%; nondippers, 7.6%; and reverse-dippers, 22%), and this remained significant in a Cox regression analysis after controlling for age, gender, body mass index, 24-hour systolic blood pressure, and antihypertensive medication. Intracranial hemorrhage was more common in reverse-dippers (29% of strokes) than in other subgroups (7.7% of strokes, \( P = 0.04 \)). In the extreme-dipper group, 27% of strokes were ischemic strokes that occurred during sleep (versus 8.6% of strokes in the other 3 subgroups, \( P = 0.11 \)). In conclusion, in older Japanese hypertensive patients, extreme dipping of nocturnal blood pressure may be related to silent and clinical cerebral ischemia through hypoperfusion during sleep or an exaggerated morning rise of blood pressure, whereas reverse dipping may pose a risk for intracranial hemorrhage. (Hypertension. 2001;38:852-857.)

Key Words: elderly • circadian rhythm • stroke • cerebral ischemia • blood pressure monitoring, ambulatory

The introduction of ambulatory blood pressure (BP) monitoring (ABPM) techniques has provided unique information about the diurnal variation of BP.1 In normal subjects, BP decreases during sleep by 10% to 20% and increases promptly upon waking. In hypertensive patients, this normal diurnal BP variation pattern is usually preserved, particularly when there is no target organ damage. However, a variety of abnormal diurnal variation patterns have been described in which the nocturnal fall of BP may be >20% (extreme-dippers), <10% (nondippers), or even reversed (reverse-dippers). These variations are of interest because they may be related to hypertensive target organ damage or to poor cardiovascular prognosis. In several cross-sectional studies, nondippers have been reported to have more clinical and subclinical target organ damage in the heart, brain, and kidneys than do dippers.2–3 Additionally, in 3 prospective studies using ABPM,4–7 2 reported that the nondipping or reverse-dipping pattern of nocturnal BP was an independent predictor for cardiovascular disease,4–6 and the third reported that nocturnal BP was closely associated with cardiovascular disease.7 We recently identified extreme-dippers, characterized by a marked nocturnal BP fall, and studied the mechanism of this condition.8–12 In an analysis of approximately the first 30% of subjects recruited for the present study, elderly hypertensive patients who were extreme dippers had an increased prevalence of silent cerebrovascular disease (silent cerebral infarcts [SCI] and advanced deep white matter ischemic lesions),8 raising the possibility that nocturnal cerebral hypoperfusion might be a risk factor for cerebrovascular disease. SCI is a specific marker of target organ damage in the brain and a powerful predictor of stroke.13 Thus, it is reasonable to suppose that patients with SCI who are extreme-dippers may be more prone to develop a stroke when treated with antihypertensive therapy. It has also been reported that extreme-dippers with coronary artery disease demonstrated an increase of nocturnal silent myocardial ischemia when they were treated with antihypertensive therapy.14 However, there is no prospective study on the cardiovascular prognosis of extreme-dipping status in older hypertensive patients.

To test our hypothesis that marked changes in diurnal hemodynamic variation can trigger stroke events, we have

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From the Department of Cardiology, Jichi Medical School (K.K., S.H., K.S.), Tochigi, Japan; Department of Internal Medicine, Hyogo Prefectural Awaji Hospital (T.M.), Hyogo, Japan; The Zena and Michael A. Weiner Cardiovascular Center, Mount Sinai School of Medicine (K.K., T.G.P.), NY; Department of Psychiatry and Behavioral Science, State University of New York at Stony Brook (J.E.S.).

Correspondence to Kazuomi Kario, MD, PhD, FACC, FACP, Department of Cardiology, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Kawachi, Tochigi, 329-0498, Japan. E-mail kkario@jichi.ac.jp

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investigated the consequences of different patterns of diurnal BP variation on silent and clinically overt cerebrovascular disease in older patients with sustained hypertension.

Methods

Patients
This study is based on 575 elderly patients with sustained hypertension who satisfied the following criteria: (1) essential hypertension with average clinic BP ≥140 mmHg for systolic (SBP) and/or ≥90 mm Hg for diastolic BP (DBP) on ≥2 occasions; (2) average 24-hour ambulatory BP ≥130 mmHg for systolic or >80 mm Hg for diastolic;15 (3) age ≥50 years. Thus, patients with white-coat hypertension (WCHT) were excluded. No patient took antihypertensive medication during the 14 days before the ABPM study, although 57% had a prior history of antihypertensive medication use. Electrocardiographically-verified left ventricular hypertrophy (ECG-LVH) was defined by abnormally high voltages of QRS-complexes (R in V_5 plus S in V_1 ≥3.5 mV) associated either with flat T-waves (<10% of R) or with ST-segment depression and biphasic T-waves.

24-Hour ABPM
Noninvasive ABPM was performed on a weekday with an automatic device, which recorded BP (by the oscillometric method) and heart rate every 30 minutes for 24 hours. Sleep BP was defined as the average of BP measurements from the time when the patient went to bed until the time he/she got out of bed; and awake BP, as the average of BP measurements recorded during the rest of the day. The nocturnal SBP fall (%) was calculated as 100×[1−sleep SBP/awake SBP ratio]. We subclassified the patients by the nocturnal SBP fall as follows: extreme dippers if the nocturnal SBP fall was ≥20%, dippers if the fall was ≥10% but <20%, nondippers if it was ≥0% but <10%, and reverse dippers if it was <0%. In our earlier study of elderly hypertensive outpatients that included extreme-dippers and reverse-dippers, the nocturnal BP fall exhibited relatively good reproducibility.16

Brain Magnetic Resonance Imaging
Of the 575 patients, 361 (63%) agreed to and had brain magnetic resonance imaging (MRI) using a superconducting magnet with a main strength of 1.5T within 3 months of their ABPM. A SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images, as described previously.3,8 Multiple SCIs were defined as images that was also visible as a hyperintense lesion on T2-weighted images, with average clinic BP ≥140 mm Hg for diastolic BP (DBP) on ≥2 occasions; (2) average 24-hour ambulatory BP ≥130 mmHg for systolic or >80 mm Hg for diastolic;15 (3) age ≥50 years. Thus, patients with white-coat hypertension (WCHT) were excluded. No patient took antihypertensive medication during the 14 days before the ABPM study, although 57% had a prior history of antihypertensive medication use. Electrocardiographically-verified left ventricular hypertrophy (ECG-LVH) was defined by abnormally high voltages of QRS-complexes (R in V_5 plus S in V_1 ≥3.5 mV) associated either with flat T-waves (<10% of R) or with ST-segment depression and biphasic T-waves.

Follow-Up and Events
The patients’ medical records have been intermittently reviewed after ABPM for the use of antihypertensive drug therapy and the occurrence of cardiovascular events. Follow-up was performed during a 20-month period from 1996 to 1998; the mean follow-up period was 41-months, with a range from 1 to 68 months. Cardiovascular events were diagnosed by each physician who cared for patients at the time of events, and classified as cardiac events, stroke events, and noncardiovascular deaths. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. A sleep-onset stroke was defined as one that occurred between the time of going to bed and waking up. Cardiac mortality includes fatal myocardial infarction and unexplained sudden death.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Results

Baseline Characteristics and Silent Cerebral Infarcts
The distribution of dipping patterns in the study patients were as follows: extreme-dippers, 17%; dippers, 40%; nondippers, 32%; and reverse-dippers, 11% (Table 1). The mean age was higher and BMI was lower in reverse-dippers than in extreme-dippers and dippers. A family history of hypertension was significantly less common in the dippers than in the other 3 groups (all, \(P<0.05\)), and a family history of cardiovascular disease was significantly more common in reverse-dippers than in dippers (\(P=0.007\) or nondippers (\(P=0.03\)). There were no significant differences in clinic BPs among the groups, although 24-hour SBP was significantly lower in extreme-dippers than in the other groups (all, \(P<0.02\)), and higher in reverse-dippers than in dippers (\(P=0.008\) and nondippers (\(P=0.05\). There was no significant difference in awake BPs between extreme-dippers and dippers, whereas awake BPs were lower in nondippers and reverse-dippers than extreme-dippers and dippers (all, \(P<0.001\). The largest differences were in sleep SBP, where all pairwise differences were significant (all, \(P<0.001\). The results for DBP are similar except that there were no group differences in 24-hour DBP.

Figure 1 shows a U-shaped association between dipping status and SCIs, with an excess of events in the 2 extremes of dipping (extreme-dippers and reverse-dippers). The prevalence of SCIs and multiple SCIs was significantly higher in extreme-dippers than in dippers, and multiple SCIs were also more common in reverse-dippers than in dippers.

Stroke Incidence
There were 54 stroke events during the follow-up period (23 477 person-months; average, 41 month/person). There was a significant J-shaped relationship between the incidence of stroke (both nonfatal and total events) and dipping status (Figure 2). The reverse-dippers had the worst stroke prognosis, and extreme-dippers had the second worst prognosis, whereas there was no significant difference between dippers and nondippers (Figures 2 and 3). In the Cox regression analysis (Table 2), age (RR, 1.80 for a 10-year increase; \(P=0.0003\), male gender (RR, 1.80; \(P=0.03\), 24-hour SBP (RR, 1.29 for a 10-mm Hg increase; \(P=0.007\), and dipping status \((\chi^2=7.9, df=3, P=0.05\) for global test of group differences) were independent predictors of stroke events (model 1). Examination of pairwise group differences indicated that extreme-dippers were at greater risk than were dippers (RR, 2.32, \(P=0.03\) and nondippers (RR, 2.33; \(P=0.04\) and there was a tendency for reverse-dippers to also be at greater risk than dippers (RR, \(2.05; P=0.07\) and nondippers (RR, 2.06; \(P=0.06\). In model 2 (Table 2), in which the other cardiovascular risk factors were entered, current smoking status was an independent predictor for stroke (RR, 2.15; \(P=0.015\), but the results from model-1 were essentially unchanged. When we added ECG-LVH to model 2, the RR of ECG-LVH was 4.2 (\(P=0.0001\); however, the global \(P\) value for dipping status was 0.03, with
extreme-dippers being at greater risk than dippers (RR, 2.6; \( P \leq 0.02 \)). When we used DBP to classify dipping status in models 1 and 2, the results were essentially the same (global \( P = 0.015 \) for model 1; \( P = 0.023 \), for model 2).

Cardiovascular Mortality
There was no J-shaped relation between fatal stroke events and dipping status (Figure 2). The fatal stroke incidence was significantly higher in reverse-dippers than in the other 3 groups combined (\( P = 0.02 \)). There was a monotonic relationship be-

TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Measures</th>
<th>Extreme-Dippers (n=97)</th>
<th>Dippers (n=230)</th>
<th>Nondippers (n=185)</th>
<th>Reverse-Dippers (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 \pm 9.2</td>
<td>72 \pm 10</td>
<td>73 \pm 9.3*</td>
<td>77 \pm 9.5†‡§</td>
</tr>
<tr>
<td>Male, %</td>
<td>38</td>
<td>39</td>
<td>40</td>
<td>51</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.5 \pm 3.6</td>
<td>24.3 \pm 3.7</td>
<td>23.7 \pm 3.7</td>
<td>22.7 \pm 3.6|</td>
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<td>Current smoker, %</td>
<td>21</td>
<td>19</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Family history (either parent), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>20*</td>
<td>30†</td>
<td>38|</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>24</td>
<td>19</td>
<td>22</td>
<td>37|#</td>
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<tr>
<td>Diabetes, %</td>
<td>13</td>
<td>12</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>17</td>
<td>19</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>ECG-LVH, %</td>
<td>18</td>
<td>17</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>167 \pm 20</td>
<td>168 \pm 19</td>
<td>167 \pm 18</td>
<td>170 \pm 21</td>
</tr>
<tr>
<td>24-Hour</td>
<td>142 \pm 9.9</td>
<td>145 \pm 12*</td>
<td>146 \pm 13|</td>
<td>150 \pm 15|#</td>
</tr>
<tr>
<td>Awake</td>
<td>157 \pm 12</td>
<td>154 \pm 14</td>
<td>150 \pm 14\†</td>
<td>147 \pm 16\†</td>
</tr>
<tr>
<td>Sleep</td>
<td>118 \pm 11</td>
<td>131 \pm 12†</td>
<td>140 \pm 13\†</td>
<td>152 \pm 15\†*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>94 \pm 14</td>
<td>95 \pm 13</td>
<td>92 \pm 14</td>
<td>92 \pm 15</td>
</tr>
<tr>
<td>24-Hour</td>
<td>81 \pm 6.4</td>
<td>82 \pm 8.6</td>
<td>82 \pm 8.8</td>
<td>83 \pm 9.1</td>
</tr>
<tr>
<td>Awake</td>
<td>89 \pm 7.3</td>
<td>87 \pm 9.2</td>
<td>83 \pm 9.5\†</td>
<td>83 \pm 9.0\†</td>
</tr>
<tr>
<td>Sleep</td>
<td>69 \pm 7.0</td>
<td>74 \pm 8.0†</td>
<td>79 \pm 9.3\†</td>
<td>84 \pm 10\†*</td>
</tr>
<tr>
<td>Nocturnal SBP dipping, %</td>
<td>25 \pm 5.2</td>
<td>15 \pm 2.7†</td>
<td>6.3 \pm 2.9\†</td>
<td>-3.7 \pm 4.5\†*</td>
</tr>
<tr>
<td>Duration of follow-up, months</td>
<td>41 \pm 14</td>
<td>40 \pm 14</td>
<td>42 \pm 13</td>
<td>41 \pm 14</td>
</tr>
</tbody>
</table>

Data are shown as mean \( \pm \)SD or percentages.
Overall \( P \) values for 4-group comparison of means (ANOVA F-test) or percentages (\( \chi^2 \) test).
*\( P < 0.05 \), \|\( P < 0.01 \), †\( P < 0.001 \) vs extreme dippers. \|\( P < 0.01 \), †\( P < 0.001 \) vs dippers. \#\( P < 0.05 \), §\( P < 0.01 \), **\( P < 0.001 \) vs nondippers.
between cardiovascular mortality (fatal stroke and cardiac events) and dipping status (extreme-dippers, 1.0%; dippers, 2.6%; non-dippers, 2.7%; and reverse-dippers, 11%) (P < 0.004). Cardiovascular mortality was significantly higher in reverse-dippers than in the 3 other dipping status groups combined (RR, 5.2; P < 0.002). After controlling for the confounders listed in model 1 (Table 2), the RR of reverse-dippers for fatal cardiovascular events was 1.6 (not significant).

Effect of Silent Cerebral Infarcts

We divided the 361 patients who had brain MRIs into 2 groups: those with no SCIs (n = 169) and those with ≥1 SCIs (n = 192). Stroke incidence was much higher in the latter group than in the 3 other dipping status groups combined (RR, 5.2; P = 0.002). After controlling for the confounders listed in model 1 (Table 2), the RR of reverse-dippers for fatal cardiovascular events was 1.6 (not significant).

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Stroke Subtype
Of the 54 stroke events, 35 were ischemic strokes, 7 were hemorrhagic strokes, and 12 were unknown (Figure 4). The percentage of strokes that were hemorrhagic was 29% in reverse-dippers but only 7.5% in the other 3 groups (P = 0.04). Dipping status tended to be monotonically associated with the prevalence of ischemic stroke, although the correlation coefficient did not reach statistical significance (P = 0.15).

Onset Time of Stroke
We identified the onset time of stroke in 46 of the 54 events. Between 40 and 55% of strokes in each group occurred in the morning period (6:00 AM to noon). Seven strokes occurred during sleep, comprising 15% of the 46 strokes for which the onset time was known. Six of these 7 sleep-time strokes were ischemic, and only 1 was a cerebral hemorrhage, which occurred in a reverse-dipper. In extreme-dippers, 27% of strokes were ischemic strokes that occurred during sleep, whereas only 8.6% of strokes in the other 3 subgroups were of this type (P = 0.11).

Discussion
This study found that there were differences in the prevalence of SCIs and the incidence of strokes in a population of elderly hypertensives according to the dipping status of nocturnal BP. There was a J-shaped relationship between nocturnal dipping status and stroke incidence, such that reverse-dippers (with a nocturnal increase in BP) and extreme-dippers (with marked nocturnal BP falls) had worse prognoses than dippers or nondippers. We used SBP for the definition of dipping status, because the clinical significance of SBP is greater than DBP in older patients and 24-hour SBP was more closely correlated with stroke events than 24-hour DBP in this study. However, when we used DBP to classify dipping status, the results were essentially the same.

Reverse-Dippers
The reverse-dippers had the highest incidence of strokes. They were older, more likely to be male, and had a higher 24-hour SBP than did the other 3 groups. These factors were all independently associated with stroke prognosis (Table 2, Model-1). Thus, the poorer prognosis of reverse-dippers may partly be explained by these confounding factors. We also added other major cardiovascular risk factors (diabetes, hyperlipidemia, and current smoking status) into the Cox regression model (Table 2, Model-2) and found that current smoking status was an independent predictor of stroke. However, after controlling for these factors, reverse-dippers still had approximately twice the risk for stroke that dippers or nondippers had. Hemorrhagic stroke was relatively more common in reverse-dippers, although 83% of all their strokes occurred during the awake period. This suggests that the higher sleep BP level per se may not be the main cause for the strokes in reverse-dippers. In a previous study, reverse-dippers also had twice as many total cardiovascular events (cardiac and stroke events) as the other dipping groups.

Extreme-Dippers
Extreme-dippers also had a worse prognosis than that of dippers. These results suggest that cerebral hypoperfusion due to the nocturnal BP fall might trigger ischemic strokes during the night in extreme-dippers. On the other hand, in the present study, 55% of strokes in extreme-dippers occurred in the morning period, suggesting that the exaggerated morning rise of BP in extreme-dippers might also contribute to stroke events. Further analysis of onset time of the stroke events in relation to stroke subtype in a larger prospective study is necessary to clarify the impact of extreme dipping status on nocturnal events.

Cardiovascular Mortality
We did not find an increased risk of stroke or cardiovascular mortality in extreme-dippers. On the other hand, both stroke mortality and cardiovascular mortality were increased in reverse-dippers. This result is consistent with a previous Japanese report, although the study design and population of our study (clinic-based hypertensive patients with a mean age of 72 years) were quite different from those of the previous study (community-based sample with a mean age of 62 years). Thus, there is a possibility that the relationship between stroke and dipping status is different between stroke morbidity (the J-curve relationship) and mortality (a monotonic relationship). This difference may depend on different mechanisms underlying strokes in each dipping group. Thus, strokes of extreme-dippers may be minor ischemic strokes that are rarely fatal, whereas in reverse-dippers they may tend to be major ischemic or hemorrhagic strokes that are more often fatal.

Silent Cerebral Infarcts
As SCI is considered to be the most specific preclinical marker of target organ damage for stroke, we assessed its presence at baseline using brain MRI in 61% of the study sample. We essentially confirmed our previous finding that SCIs were more common in extreme-dippers and the combined group of nondippers and reverse-dippers than in dippers. In this study, this association was clearly found only for multiple SCIs. During the follow-up period, the stroke incidence was approximately 5 times higher in those who had SCIs at baseline than in those without any SCIs.

Racial Difference
There are marked differences in the epidemiology of cardiovascular disease between Japan and the USA or European countries. Among Japanese, coronary artery disease is much less common, whereas stroke is more common than among whites or blacks. Both environmental and genetic factors probably contribute to these differences. Regardless of the explanation, further research is needed to determine whether the present findings generalize to other populations.

Study Limitations
The findings presented above ignore the possible confounding effect of antihypertensive medications. Although we have data on medication status at the time of follow-up, we inadvertently failed to obtain medication data for the time...
period between the ambulatory BP assessment and the final follow-up evaluation. Therefore, we are unable to adjust for the possibilities that some persons may only have been on medication for a short time at the follow-up examination, whereas others could have been taking medication for much of the follow-up period but be off medication at the time of the follow-up. Given that medication status at follow-up did not predict stroke events ($P \geq 0.20$), it is unlikely that a more comprehensive medication measure would substantially alter our results.

Despite the relatively large size of this prospective study, the number of stroke events is relatively small, especially when we are trying to draw comparisons among the 4 groups. And when we examine subtypes of stroke to try to gain some insight into possible mechanisms, the N’s are even smaller and our conclusions more speculative. Nonetheless, what we think this data set clearly shows is that the 2 extreme patterns of nocturnal dipping (extreme-dipping and reverse-dipping) are collectively associated with a more than doubling in the risk of stroke.

**Conclusion**

In this study, abnormal diurnal BP variation patterns (extreme dipping and reverse dipping) are independent predictors of stroke in elderly Japanese patients with sustained hypertension. This finding that marked changes in diurnal hemodynamic variation predict stroke events should be investigated in other racial populations and in a large randomized controlled trial using antihypertensive medication.

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**References**

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