Diuretics Shift Circadian Rhythm of Blood Pressure From Nondipper to Dipper in Essential Hypertension

Takashi Uzu, MD; Genjiro Kimura, MD

Background—Recently, we found that sodium restriction shifted the circadian rhythm of blood pressure from nondipper to dipper in patients with the sodium-sensitive essential hypertension. This study examined whether diuretics can transform the circadian rhythm of blood pressure from nondipper to dipper.

Methods and Results—We studied 21 patients with essential hypertension during both a baseline period and a period of treatment with hydrochlorothiazide (25 mg daily). The periods lasted 4 weeks each. Twenty-four hour ambulatory blood pressures were measured on the same day of the week at the end of each period. In nondippers (n=11), but not in dippers (n=10), a significant interaction existed between diuretic therapy and nocturnal fall in systolic and diastolic blood pressure, which indicated that the degree of nocturnal blood pressure fall was affected by diuretic therapy. Nocturnal fall, which was diminished in nondippers, was restored by diuretic therapy with hydrochlorothiazide, indicating that the circadian rhythm of blood pressure shifted from nondipper to dipper patterns.

Conclusions—The present study demonstrated that diuretics can restore nocturnal blood pressure decline in a manner similar to sodium restriction, which suggests that the kidneys and sodium metabolism may play important roles in the genesis of the circadian rhythm of blood pressure. Diuretic-based treatment may have an additional therapeutic advantage of reducing the risk for cardiovascular complications by transforming the circadian rhythm of blood pressure.

Key Words: blood pressure circadian rhythm diuretics kidney

In patients with essential hypertension, it has been postulated that the lack of nocturnal blood pressure (BP) fall (nondipper) is associated with more serious end-organ damage1,2 than occurs in patients whose BP falls during the night (dipper). Recently, we found that BP failed to fall during the night in patients with sodium-sensitive essential hypertension,3 and we also showed that sodium restriction shifted the circadian rhythm of BP from nondipper to dipper in these patients.4 We previously showed that mefruside, a diuretic, lowered BP in patients with a high sodium sensitivity, mainly by making the BP sodium insensitive.5 These findings suggested that diuretics might restore the nocturnal fall of BP in patients with nondipper hypertension by reducing the sodium sensitivity of their BP. The diuretic-based treatment of patients with hypertension prevents the development of cardiovascular complications,6,7 and diuretics have been recommended as 1 of the first-choice medications in the management of hypertension.8 One of possible mechanisms of how diuretics relieve cardiovascular overload may be the normalization of circadian BP rhythm.

In this study, therefore, we examined the effect of hydrochlorothiazide on the circadian BP rhythm in patients with essential hypertension who were classified into 2 groups according to the degree of their nocturnal BP reduction.

Methods

Patients
We studied 21 Japanese outpatients with essential hypertension at the National Cardiovascular Center Hospital in Osaka, Japan (8 men and 13 women aged 45 to 69; mean age, 60±7 years), all of whom had given their informed consent. Hypertension was defined as a systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg on at least 3 different visits to outpatient clinics of the hospital (office BP readings were used). Patients were excluded if they had a history of cardiac disease, stroke, hepatic disease, renal disease, or diabetes mellitus.

Study Protocol
After the 6- to 12-week run-in period during which BP was recorded by mercury sphygmomanometer in the sitting position, patients were subjected to the respective study protocols. Previous antihypertensive drugs were withdrawn before the study, and any other medication was maintained at the same dosage throughout the study. The patients entered a baseline period without antihypertensive drugs lasting for 4 weeks, and then a diuretic, hydrochlorothiazide, was administered for 4 weeks. No placebo was given during the baseline period, and patients received 25 mg of hydrochlorothiazide at 7:00 AM during the treatment period. Twenty-four hour ambulatory BPs were measured every half-hour noninvasively with an automatic device (model ES-A531, Terumo) on the same day of the week at the end of the each period. The mean arterial pressure (MAP) was calculated as the diastolic BP plus 1/3 of pulse BP. The daytime BP

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1635
was calculated as the average of the 33 readings between 6:00 AM and 10:30 PM, and nighttime BP was the average of the remaining 15 readings. The nocturnal fall in MAP was calculated as the difference between daytime and nighttime MAP. Patients whose nocturnal fall in MAP was more than 10% from day to night during the baseline period were classified as dipper, whereas the remaining patients were classified as nondipper, as described in our previous report.9 Blood samples were collected at the end of the baseline period.

### Statistical Analysis

Results are expressed as mean±SD. Significances of differences in parameters between dippers and nondippers were determined by Student’s t test for nonpaired samples and by χ² test when appropriate. The significance of the effects of diuretic therapy and nocturnal fall on BP and their interaction were tested by 2-way ANOVA and ANCOVA with repeated measures. The presence of the alternating action by this analysis was considered evidence of an interaction between diuretic therapy and nocturnal fall. The significance of difference in BP and heart rate between dippers and nondippers was also tested by 2-way ANOVA.

### Results

Among the 21 patients with essential hypertension, 10 were classified as dipper and 11 as nondipper. The baseline clinical characteristics of the studied patients are summarized in Table 1. No significant differences were detected in age, sex, body mass index, serum creatinine, plasma renin activity, or aldosterone concentration between the 2 types.

The average values of BP during the day and night, before and after diuretic therapy, are shown in Table 2. During the baseline period, daytime BP values were all higher and nighttime BP values were all lower in dippers than in nondippers. Hydrochlorothiazide therapy significantly lowered only systolic BP in dippers, whereas it lowered both systolic and diastolic BP in nondippers. Nocturnal falls of MAP from day to night were significant in both groups, although during the baseline period, the degree of nocturnal MAP fall was significantly greater in dippers than in nondippers (20±10 versus 3±5 mm Hg, respectively; P<0.001). In nondippers, but not in dippers, a significant interaction existed between diuretic therapy and nocturnal fall in systolic and diastolic BP, indicating that degree of nocturnal BP fall was affected by diuretic therapy. In dippers, heart rates during the day and night were as follows: baseline, 75±13 and 64±11 bpm, respectively; diuretic therapy, 73±14 and 62±13 bpm, respectively. Heart rates during the day and night in nondippers were as follows: baseline, 71±15 and 60±12 bpm; diuretic therapy, 74±14 and 65±13 bpm, respectively. In both types of essential hypertension, heart rates were significantly (P<0.001) reduced from day to night.

The Figure compares the effects of diuretic therapy and nocturnal fall on MAP and the interaction of these variables between dippers and nondippers in dippers, nocturnal MAP fall was not affected by hydrochlorothiazide therapy. In nondippers, however, nocturnal MAP fall was significantly enhanced by diuretic therapy; an interaction (alternating action, P<0.001) existed between the effects of diuretic therapy on MAP and nocturnal fall. These findings showed that nocturnal fall, which was diminished in nondippers, was restored by diuretic therapy, indicating that the circadian rhythm of BP shifted from nondipper to dipper patterns. However, the nocturnal fall of dippers was not affected.

### Discussion

In the present study, we clearly showed that nocturnal fall in BP was restored by therapy with diuretics in nondippers, indicating that the circadian rhythm of BP was transformed from nondipper to dipper patterns by diuretics. However, nocturnal fall was not affected by diuretic therapy in dippers. Recently, we found that BP failed to fall during the night in patients with sodium-sensitive essential hypertension.3 This

### Table 1. Clinical Findings of Studied Patients with Essential Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Dippers (n=10)</th>
<th>P</th>
<th>Nondippers (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50±7</td>
<td>0.89</td>
<td>52±8</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>5/5</td>
<td>0.28</td>
<td>3/8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.9±2.9</td>
<td>0.82</td>
<td>22.6±3.3</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.7±0.2</td>
<td>0.79</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/mL⁻¹ . h⁻¹</td>
<td>1.0±0.8</td>
<td>0.47</td>
<td>0.8±0.7</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>11.3±5.7</td>
<td>0.43</td>
<td>13.7±7.7</td>
</tr>
</tbody>
</table>

Values are mean±SD or no. of patients (%).

### Table 2. Day–Night Blood Pressure and Heart Rate During Baseline and Diuretic Treatment Periods

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Diuretics</th>
<th></th>
<th>Effect of Nocturnal Fall</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Night</td>
<td>Day</td>
<td>Night</td>
<td></td>
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<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dippers</td>
<td>144±20</td>
<td>121±18</td>
<td>135±22</td>
<td>117±21</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dippers</td>
<td>140±21</td>
<td>137±18</td>
<td>132±19</td>
<td>120±17</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dippers</td>
<td>93±11</td>
<td>77±12</td>
<td>93±17</td>
<td>77±15</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dippers</td>
<td>88±12</td>
<td>85±13</td>
<td>85±13</td>
<td>73±12</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Results were analyzed based on 2-way ANOVA with repeated measures; BP was measured 33 times for daytime values (from 6 AM to 10:30 PM) and 15 times for nighttime values (from 11 PM to 5:30 AM). Data are expressed as mean±SD.
Effects on MAP of diuretic therapy with hydrochlorothiazide, nocturnal fall, and their interaction in dippers (left) and nondippers (right). Two-way ANCOVA and ANCOVA with repeated measures clearly demonstrated the presence of an interaction (alternating action, \( P < 0.001 \)) only in nondippers, indicating that diminished nocturnal BP decline was restored by hydrochlorothiazide therapy, and circadian rhythm of BP shifted from nondipper to dipper. ○ and □, MAP values during baseline and diuretic treatment periods, respectively. Error bars indicate either upper or lower half of 95% confidence interval.

was recently confirmed by other authors.\(^{10}\) We also showed that sodium restriction shifted the circadian rhythm of BP from nondipper to dipper in these patients.\(^{4}\) The diurnal rhythm of BP was also disturbed in patients with primary aldosteronism, a typical form of sodium-sensitive secondary hypertension, and sodium restriction enhanced nocturnal BP fall in these patients as well.\(^{11}\) There are other sodium-sensitive types of hypertension, such as hypertension in blacks,\(^{9,12}\) glomerulonephritis,\(^{13}\) and patients with diabetes mellitus.\(^{14,15}\) The diurnal rhythm of BP is also reported to be disturbed in these pathophysiological states.\(^{16–18}\) Thus, regardless of the mechanism of sodium sensitivity of BP, whether the ultrafiltration coefficient was reduced or tubular sodium reabsorption was enhanced,\(^{19}\) nocturnal BP fall diminished in all patients with sodium-sensitive types of hypertension who had relatively high sodium intake. We previously reported that a diuretic, mefruside, lowered BP, especially in patients with high sodium sensitivity, by reducing their sodium sensitivity.\(^{5}\) Therefore, we examined the effects of the diuretic hydrochlorothiazide and found that it transformed the circadian rhythm of BP from nondipper to dipper.

It is reported that the antihypertensive response to diuretic therapy differs on the basis of the patient’s classification as dipper or nondipper.\(^{20}\) These authors also showed that hydrochlorothiazide effectively lowered 24-hour BP in nondippers and blacks, whose elevated salt sensitivity has been previously described.\(^{3,4,9,10,12}\) In the present study, similar to the previous report,\(^{20}\) the response to hydrochlorothiazide therapy in nondippers was greater than that in dippers. These findings, together with the present study, indicate that diuretics lower nighttime BP, especially in salt-sensitive hypertensives, and shift the circadian rhythm of BP in these patients from nondipper to dipper. Hydrochlorothiazide is thought to exert its hypotensive efficacy through a combined vasodilator and diuretic effect. However, the vascular action of hydrochlorothiazide in humans is reported to be small, and it occurs only at concentrations higher than those normally reached with oral treatment.\(^{21}\) Because we treated patients with a relatively lower dose (25 mg daily) of hydrochlorothiazide in this study, the hypotensive effect of hydrochlorothiazide seemed to be based on its diuretic action on the kidney. In our previous report,\(^{4}\) sodium restriction (mean reduction in sodium intake of 176 mmol/day) lowered 24-hour MAP \( \approx 16.9 \) mm Hg in patients with salt-sensitive essential hypertension. In this study, the mean value of 24-hour MAP reduction with 25 mg of hydrochlorothiazide was 7.8 mm Hg. Thus, adding 25 mg of hydrochlorothiazide may have a similar effect as a reduction in sodium intake of roughly 82 mmol/day in patients who are nondippers and/or have salt-sensitive essential hypertension.

Recently, we examined the circadian rhythm of urinary sodium excretion and the effects of sodium restriction on it in both dipper and nondipper types of essential hypertension. We found the circadian rhythm of natriuresis is disturbed in nondippers.\(^{9}\) These findings indicated that renal sodium handling may play a key role in determining the circadian rhythm of BP. When sodium intake is relatively high, the defect in sodium excretory capability becomes evident, which elevates BP at night to compensate for diminished natriuresis during the day and to cause enhanced-pressure natriuresis at night. When sodium intake is low, however, the defect remains latent, allowing BP to lower at night. These speculations, together with the well-known fact that in patients with renal dysfunction, nocturnal BP fall is lost,\(^{22–24}\) suggest that the circadian rhythm of BP is determined, at least in part, by the kidneys. The importance of the kidneys in the genesis of circadian BP rhythm is consistent with a recent report determining that the circadian rhythm of BP normalizes after kidney transplantation.\(^{25}\) These findings forced us to postulate that a renal defect in excreting sodium into the urine and the resulting sodium retention might be important determinants for impairments in nocturnal BP fall. The fact that diuretic therapy normalized the circadian BP rhythm of nondippers also supports the importance of the kidney and its sodium excretory capability in the loss of nocturnal BP dip.

In patients with essential hypertension, it has been proposed that the lack of the nocturnal fall in BP is associated with more serious end-organ damage.\(^{1,2}\) Patients with a sodium-sensitive type of essential hypertension are also more likely to manifest end-organ damages, such as left ventricular hypertrophy and microalbuminuria, than those who do not have the sodium-sensitive type.\(^{26}\) Furthermore, we found the sodium sensitivity of BP was an independent cardiovascular risk factor in patients with essential hypertension.\(^{27}\) Diuretic-based treatment of patients with hypertension prevents the development of cardiovascular complications.\(^{6,7}\) and diuretics have been recommended as 1 of the first-choice medications for the management of hypertension.\(^{8}\) Diuretic-based therapy may relieve these cardiovascular risks by systemic BP reduction and the normalization of the circadian BP rhythm.

In conclusion, the present study demonstrated for the first time that the nocturnal BP decline, which is diminished in patients with the nondipper type of essential hypertension,
was restored by diuretic therapy with hydrochlorothiazide, and their circadian rhythm of BP shifted from nondipper to dipper. Diuretic-based treatment may have an additional therapeutic advantage by reducing the risk of cardiovascular complications by transforming the circadian rhythm of BP.

References

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