Calcium Channel Blockers Shorten the Periodicity of Ultradian Variation in Blood Pressure in Patients with Essential Hypertension

Hiroshi Kawamura, Hiromi Mitsubayashi, Tomoaki Saito*, Katsuo Kanmatsuse**, and Noboru Saito***

We studied ultradian and circadian variations in blood pressure (BP) in patients with essential hypertension who were receiving antihypertensive agents. No patient had previously received antihypertensive agents before this study began. After a 2-wk control period, we performed ambulatory blood pressure monitoring (ABPM) in 86 patients with essential hypertension (WHO stages I or II). The patients were then given a long-acting angiotensin converting enzyme inhibitor (ACEI) (captopril or imidapril), a β-receptor blocker (aro-tilol or bisoprolol), or a calcium channel blocker (nisoldipine or bendipine) twice daily to control BP. We evaluated the patients’ BP once every 2 wk to ensure optimal control. After 12 wk, ultradian and circadian variations in BP were analyzed by the maximum entropy method (MEM). All antihypertensive agents decreased office systolic BP (SBP), office diastolic BP (DBP), 24-h SBP, and 24-h DBP. ACEI did not change office, 24-h, daytime, or nighttime pulse rate (PR). Arotilol and bisoprolol decreased 24-h PR. All antihypertensive agents decreased 24-h, daytime, and nighttime pressure rate product. MEM showed that no antihypertensive agent affected the circadian variation in the 1st peak (24-h periodicity) of SBP, DBP, or PR. However, calcium channel blockers shortened the periodicity of circadian variations in the 2nd peak (12-h periodicity) of SBP and the 3rd peak (8 to 6 h periodicity) of SBP. Therefore, ultradian variations in BP should be carefully monitored in hypertensive patients treated with calcium channel blockers. (Hypertens Res 1998; 21: 179-186)

Key Words: circadian rhythm, blood pressure, antihypertensive agents

Ambulatory blood pressure monitoring (ABPM) enables us to study circadian variation in blood pressure (BP). Previously we reported that the periodicity of variation in diastolic blood pressure (DBP) (24-h periodicity) was shortened in patients treated with nicardipine. However, ultradian variation in BP has not been studied in detail in large numbers of hypertensive patients receiving calcium channel blockers (1). Few studies have compared different long-acting antihypertensive agents with respect to their effects on ultradian variation in BP. Most prior studies have evaluated circadian variation in BP (2–7). We therefore studied ultradian variation in BP in essential hypertensive patients treated with long-acting antihypertensive agents. We also compared ultradian and circadian variations in BP in essential hypertensive patients given antihypertensive agents with different mechanisms of action.

Subjects and Methods

Patients
We studied 86 patients with essential hypertension (38 men and 46 women; average age 53 ± 12 yr; range, 35 to 65 yr). Written informed consent was obtained from all patients. The office BP was measured at the beginning of the study and was defined as the mean of three sphygmomanometer readings taken 5 min apart with the patient in the sitting position. No patient had previously received antihypertensive agents before this study began. The study protocol followed a randomized, parallel group design. After the control BP values were obtained at the end of the control period, hypertension was diagnosed if the seated office average BP measured on three separate occasions was 160/90 mmHg or higher. Routine biochemical examinations were performed, and secondary forms of hypertension were ruled out by standard clinical procedures. All patients were found to have essential hypertension (WHO stages I or II). They had regular daily working hours (08:00 to 18:00) and were not shift workers. Before ABPM, each subject was asked to maintain the same time schedule for activities and rest for 1 wk. All patients who were unable to sleep well or who had postprandial hypotension and all

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Received March 25, 1998; accepted in revised form June 22, 1998.
women around the time of menstruation were excluded from the study. All patients were instructed to avoid bathing, napping, drinking alcohol, excessive physical activity, and mental stress during ABPM. Meals were taken between the hours of 06:00 to 8:00, 12:00 to 14:00, and 18:00 to 20:00, with no change in diet.

**Table 1. Demographic and Physiological Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Angiotensin converting enzyme inhibitors (n=27)</th>
<th>β-Receptor blockers (n=27)</th>
<th>Calcium channel blockers 1 vs. 2, 3 vs. 4, 5 vs. 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Captopril (1)</td>
<td>Arotinolol (3)</td>
<td>Nisoldipine (5) Benidipine (6)</td>
</tr>
<tr>
<td>Number</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/6</td>
<td>6/7</td>
<td>8/8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59±12</td>
<td>53±12</td>
<td>55±8</td>
</tr>
<tr>
<td>BL (cm)</td>
<td>157±7</td>
<td>164±8</td>
<td>160±6</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>52±8</td>
<td>64±11</td>
<td>58±9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5±5.9</td>
<td>24.0±3.0</td>
<td>22.5±3.5</td>
</tr>
</tbody>
</table>

BL, body length; BW, body weight; BMI, body mass index. n.s., not significant.

**Fig. 1.** The top panel shows the circadian profiles of systolic blood pressure, diastolic blood pressure, and pulse rate in hypertensive patients treated with captopril. The bottom panel shows the circadian profile of pressure rate product (PRP) in hypertensive patients treated with captopril; *p<0.05 (from the top, SBP, DBP, PR, and PRP; solid line, before treatment; dotted line, after treatment).

**Fig. 2.** The top panel shows the circadian profiles of systolic blood pressure, diastolic blood pressure, and pulse rate in hypertensive patients treated with imidapril. The bottom panel shows the circadian profile of pressure rate product (PRP) in hypertensive patients treated with imidapril; *p<0.05 (from the top, SBP, DBP, PR, and PRP; solid line, before treatment; dotted line, after treatment).
We used ABPM devices (TM2421, A&D Co., Tokyo, Japan). These ABPM devices have been validated according to either the British Hypertension Society or the Association for the Advancement of Medical Instrumentation protocol (8, 9). All measurements were made on weekdays during regular activities. Twenty-four-hour BP, daytime BP, nighttime BP, 24-h pulse rate (PR), daytime PR, and nighttime PR were defined as the means of each variable as described previously (1). Briefly, mean BP and PR values during ABPM in each subject were calculated for the entire 24 h and separately for the period between 09:00 and 17:00, designated as daytime, and for the period between 22:00 and 06:00, designated as nighttime.

**Protocol**

After control BP values were obtained at the end of the control period, we gave the patients a long-acting angiotensin converting enzyme inhibitor (ACEI) (captopril, Captoril-Retard®, Sankyo, Tokyo, or imidapril hydrochloride, Tanatoril®, Tanabe Pharm. Co., Tokyo), a long-acting β-receptor blocker (arotinolol hydrochloride, Almarl®, Sumitomo Pharm. Co., Tokyo or bisoprolol fumarate, Maintate®, Tanabe Pharm. Co., Tokyo), or a long-acting calcium channel blocker (nisoldipine, Baymycard®, Bayer Co., Tokyo, or benidipine hydrochloride, Conil®, Kyowa Pharm. Co., Tokyo) at 8:00 after breakfast and 20:00 after dinner. Patients were seen every 2 wk after the beginning of drug administration. If the office BP was high (SBP >140 mmHg, DBP >90 mmHg, or both), the dose was increased. Drug compliance was ascertained by retrieving and counting any remaining drugs. We repeated ABPM at the end of 12 wk and when either a sufficient hypotensive effect had been obtained or the dose of the assigned drug had reached the upper limit as defined by the protocol. Physical examination and blood and urine tests were also repeated after the end of 12 wk of antihypertensive treatment.
Data from 24-h measurements were averaged at 30-min intervals to obtain the mean and standard deviation (SD) for each 30-min period. We were primarily interested in three major peaks of variation of BP, e.g., 24 h, 12 h, and 8-6 h. Time series analyses of BP and PR were performed using the maximum entropy method (MEM) to detect multiple peaks of rhythms; we used a linearized version of the nonlinear least-squares method combined with MEM. The calculations were carried out with the 200/1000 MemCalc program (GMS Co., Ltd., Tokyo, Japan) (10) on a personal computer (PC98 FA, NEC, Tokyo, Japan). When difficulty was encountered in selecting the 8 h or 6 h peak, we chose the nearest peaks based on the strength of power density.

Statistical Analysis
The data are expressed as the means ± one standard deviation (SD). Conventional statistics were applied, including analysis of variance and non-parametric methods. The statistical significance of differences in BP and PR at each time point (48 points per 24 h) before and after antihypertensive treatment was examined with two-tailed paired t-tests. The level of statistical significance was set at \( p < 0.05 \).

Results
General Characteristics
The patients’ demographic characteristics are shown in Table 1. All groups were similar with respect to the number of patients, sex, age, and body length (BL). Body weight (BW) was slightly but not significantly less in captopril group than in the other groups (Table 1). Body mass index (BMI) did not differ among the groups.

Office BP and PR
Table 2 shows the dose of the antihypertensive agents, office SBP, office DBP, and office PR during
the control period (c) and treatment period (t). All antihypertensive agents decreased office SBP and office DBP and had similar antihypertensive effects. No patient reported side effects. No drug affected office PR, except for bisoprolol.

**Circadian Profiles of BP, PR, and Pressure Rate Product (PRP)**

Figures 1 and 2 show the circadian changes in SBP, DBP, PR, and PRP in the ACEI groups (captopril in Fig. 1, imidapril in Fig. 2). During both the control and treatment periods, we observed circadian variations in SBP, DBP, PR, and PRP, which rose during the daytime and fell during the nighttime. ACEI decreased SBP and DBP through the day. We observed similar circadian rhythms of SBP, DBP, and PR during both the control and treatment periods in patients given β-receptor blockers (arotinolol in Fig. 3, bisoprolol in Fig. 4). Arotinolol decreased SBP and DBP more in the daytime than in the nighttime (Fig. 3). Bisoprolol seemed to decrease SBP more in the morning. The circadian variation of PRP in patients given β-receptor blockers was suppressed as compared with those given ACEI or calcium channel blockers. We also observed circadian variations in SBP, DBP, PR, and PRP during both the control and treatment periods in patients receiving calcium channel blockers (nisoldipine in Fig. 5, benidipine in Fig. 6). Nisoldipine decreased SBP, DBP, and PRP more in the morning than in the evening. Benidipine decreased SBP and DBP more in the daytime than in the nighttime.

**Mean BP and PR**

Mean 24-h SBP, mean 24-h DBP, mean 24-h PR, and mean 24-h PRP during the control period (c) and treatment period (t) are shown in Table 3. All antihypertensive agents decreased mean 24-h SBP, mean 24-h DBP, and 24-h PRP. However, ACEI (captopril, and imidapril in Table 3) and calcium channel blockers (nisoldipine, and benidipine in Table 3) did not change 24-h PR. β-receptor blockers decreased 24-h, daytime, and nighttime PR (arotinolol and bisoprolol in Table 3), except for arotinolol, which did not decrease nighttime PR (arotinolol in Table 3). All antihypertensive agents decreased daytime and nighttime SBP and DBP, except for bisoprolol, which did not decrease daytime SBP (bisoprolol in Table 3). Calcium channel blockers increased daytime PR, but not nighttime PR (nisoldipine, and benidipine in Table 3). All antihypertensive agents decreased PRP, except for nisoldipine, which did not decrease daytime PRP (nisoldipine in Table 3).

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### Table 3. Mean Blood Pressure, Pulse Rate, and Pressure Rate Product during the Control and Treatment Periods

<table>
<thead>
<tr>
<th></th>
<th>Angiotensin converting enzyme inhibitors</th>
<th>β-Receptor blockers</th>
<th>Calcium channel blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Captopril (c)</td>
<td>Imidapril (c)</td>
<td>Arotinolol (c)</td>
</tr>
<tr>
<td>24 h SBP (c)</td>
<td>141 ± 23</td>
<td>140 ± 22</td>
<td>142 ± 21</td>
</tr>
<tr>
<td>24 h DBP (c)</td>
<td>83 ± 17</td>
<td>88 ± 16</td>
<td>86 ± 15</td>
</tr>
<tr>
<td>24 h PR (c)</td>
<td>73 ± 14</td>
<td>70 ± 16</td>
<td>73 ± 15</td>
</tr>
<tr>
<td>24 h PRP (c)</td>
<td>9,902 ± 3,138</td>
<td>10,561 ± 3,219</td>
<td>10,656 ± 2,677</td>
</tr>
<tr>
<td>24 h SBP (t)</td>
<td>128 ± 25*</td>
<td>130 ± 23*</td>
<td>129 ± 22*</td>
</tr>
<tr>
<td>24 h DBP (t)</td>
<td>75 ± 17**</td>
<td>80 ± 17*</td>
<td>76 ± 16**</td>
</tr>
<tr>
<td>24 h PR (t)</td>
<td>73 ± 14</td>
<td>70 ± 16</td>
<td>73 ± 15</td>
</tr>
<tr>
<td>24 h PRP (t)</td>
<td>6,860 ± 2,345**</td>
<td>9,135 ± 2,932**</td>
<td>8,618 ± 2,631**</td>
</tr>
</tbody>
</table>

Mean 24-h SBP, mean 24-h DBP, mean 24-h PR, and mean 24-h PRP during the control period (c) and treatment period (t) are shown in Table 3. All antihypertensive agents decreased mean 24-h SBP, mean 24-h DBP, and 24-h PRP. However, ACEI (captopril, and imidapril in Table 3) and calcium channel blockers (nisoldipine, and benidipine in Table 3) did not change 24-h PR. β-receptor blockers decreased 24-h, daytime, and nighttime PR (arotinolol and bisoprolol in Table 3), except for arotinolol, which did not decrease nighttime PR (arotinolol in Table 3). All antihypertensive agents decreased daytime and nighttime SBP and DBP, except for bisoprolol, which did not decrease daytime SBP (bisoprolol in Table 3). Calcium channel blockers increased daytime PR, but not nighttime PR (nisoldipine, and benidipine in Table 3). All antihypertensive agents decreased PRP, except for nisoldipine, which did not decrease daytime PRP (nisoldipine in Table 3).
Spectral Analysis

Figure 7 shows one example of the relationship between the power spectral density and frequency (1/h) of SBP as depicted by computer. MEM analysis showed no difference in ultradian and circadian variations among the major 1st, 2nd, and 3rd peaks of SBP, DBP, and PR in patients given ACEI or β-receptor blockers. Only calcium channel blockers (nisoldipine, benidipine) shortened the periodicity of ultradian variations in the 2nd peak (12 h) of SBP (nisoldipine, 13.5 ± 4.0 vs. 10.2 ± 4.0 h, p < 0.05; benidipine, 13.8 ± 4.0 vs. 11.4 ± 1.9 h, p < 0.03) and the 3rd peak (8-6 h) of SBP (nisoldipine, 8.8 ± 2.4 vs. 6.7 ± 1.5 h, p < 0.5; benidipine, 8.4 ± 2.1 vs. 6.9 ± 1.9 h, p < 0.05) (Fig. 8).

Discussion

Our study shows that six antihypertensive agents (captopril, imidapril, arotinolol, bisoprolol, nisoldipine, and benidipine) similarly decreased SBP and DBP in essential hypertensive patients. Placebo has been reported to have no effect on the results of 24-h ABPM in hypertensive patients, and long-term placebo-controlled studies would not be ethically acceptable (11). We believe that a placebo is unnecessary when ABPM is used to study the variation in BP in patients treated with antihypertensive agents. ACEI had no effect on PR, indicating minimal effect on autonomic control of the heart. We demonstrated that calcium channel blockers increased PR during the daytime. Therefore, calcium channel blockers may not suppress cardiac sym-
pathetic nerve activity. This finding is accordance with the results of another study of calcium channel blockers (7). Calcium channel blockers decreased SBP and DBP, similar to the findings of other studies (6, 7). Bisoprolol seemed to effectively decrease nighttime BP and PR. In our study, $\beta$-receptor blockers decreased PRP more effectively than did ACEI or calcium channel blockers. This is in accord with the results of another study (12). Hourly analysis showed that $\beta$-receptor blockers decreased PRP more in the daytime than in the nighttime. This is reasonable because sympathetic activity is higher in the daytime than in the nighttime.

We used rather short time intervals for daytime (09:00 to 17:00) and nighttime (22:00 to 06:00). These short intervals may exclude the effects of individual behavioral patterns. Some investigators may object to the use of fixed periods defining the day and night and to the exclusion of transition periods in the morning and evening. However, fixed time methods are reported to be reliable when subjects go to bed and arise within well defined periods (13). We used this method because more accurate results are obtained by excluding the morning and evening transition times.

Autoregressive spectral analysis has revealed that BP variations in humans are characterized by three major peaks at about 24, 12, and 8 h (14). Another study has shown that the 24-h periodicity of BP variation can be classified into four types i.e., 24-h periodicity, 24-h + 12-h periodicity, 12-h periodicity, and complicated periodicity including 24-h, 12-h, 8-h, and 6-h periodicity (or a combination thereof) (15). It may be difficult to separate 8-h periodicity from 6-h periodicity from a practical point of view. Periodicity might be a combination of two or more types of periodicity, and different periodicities might mask each other (16). It may therefore be unfeasible to separate ultradian 8-h periodicity from 6-h periodicity, unless the mechanisms of these periodicities are fully understood. We used 8-h and 6-h ultradian variations on the basis of relative strengths of power density. We believe that 12-h, 8-h, and 6-h periodicities of BP variation might be affected by daily activities, such as sleeping, physical activities, standing, mental activity, and speaking.

Since all subjects were middle-aged, weekday workers, their sleeping patterns were similar. In this respect, they were a relatively homogeneous group. With respect to the shortening of 12-h periodicity, we do not have enough data to explain this phenomenon. We found an enhanced nocturnal decrease in BP in hypertensive patients receiving another calcium channel blocker (nifedipine) (17) and found maximal depressor responses in patients given calcium channel blockers (e.g., SBP, 118-120/...
65-70 mmHg, in Fig. 5 and 6). Calcium channel blockers were given twice daily at 8:00 and 20:00. This timing of calcium channel blocker administration might affect 12-h periodicity. In addition to 12-h periodicity, a nocturnal decrease in BP associated with calcium channel blocker treatment may also affect 8-h periodicity. The shortening of 8-h and 6-h periodicities of BP variation may be due to enhanced nocturnal depression of BP by calcium channel blockers. Shortening of 12-h and 8-h periodicities may also be caused by the local circulation. Sympathetic control of local hemodynamics, such as skin, renal, and cerebral arterial blood flow, may contribute to the shortening of ultradian rhythms, such as 12-h and 8-h periodicity. Our data show that calcium channel blockers affect ultradian variation in BP as compared with other antihypertensive agents producing similar reductions in BP.

The main limitations of the present study were the small number of patients and the 12-wk follow-up period, which may have been too short for proper evaluation of BP variation. However, we believe that these limitations did not significantly influence the outcome of the present study because shortened periodicity of BP variations was found in the present and previous findings (nicardipine).

In summary, we conclude that calcium channel blockers may shorten the ultradian periodicity of variation in SBP and DBP as compared with other types of antihypertensive agents given in equipotent doses.

Acknowledgements

We thank Miss Junko Kato for her expert technical assistance. We also thank Miss Makiko Yoneyama for her secretarial assistance in the preparation of this manuscript.

References

