Calcium channel blockers are widely used as antihypertensive drugs. However, there is some controversy as to how they should be used. Our first aim was to clarify how the dihydropyridine calcium channel blocker, benidipine, affects the quantitative relationship between blood pressure (BP) and physical activity. The second aim was to determine whether there is a relationship between systolic blood pressure (SBP) and physical activity in patients with hypertension when treating with a short-acting (nifedipine) or long-acting (benidipine) calcium channel blocker.

In Study 1, ambulatory BP and physical activity were measured simultaneously in 27 patients with hypertension before and after 6 months with benidipine. In Study 2, ambulatory BP and physical activity were measured simultaneously in 16 patients with hypertension before (placebo) and after 6 weeks of crossover treatment with nifedipine and benidipine. In Study 1, there was no difference in the SBP change caused by physical activity between the pre- and posttreatment periods. In Study 2, SBP was significantly related to physical activity in the placebo (16/16) and benidipine (16/16) groups but not in the nifedipine (12/16) group. The lowest BP during daytime and nighttime in the nifedipine group were significantly lower than those in the benidipine group. Plasma renin activity (ng/mL/h) was significantly higher in the nifedipine group (1.20 ± 1.05) than in the placebo (0.57 ± 0.59) and benidipine (0.75 ± 0.78) groups. These findings indicate that nifedipine might interfere with the adaptation mechanism of BP changed by physical activity and that the activated renin-angiotensin system might cause cardiac events. Am J Hypertens 2001;14:66-69 © 2001 American Journal of Hypertension, Ltd.

Key Words: Essential hypertension, daily physical activity, ambulatory blood pressure monitoring, nifedipine, benidipine.
at diagnosis when the patients had been free from any medicine for at least 2 weeks, and again after 6 months’ treatment with benidipine. Benidipine, commonly prescribed in Japan, is administered once daily without a remarkable fluctuation in BP.12 Benidipine was increased from 2 to 8 mg until BP was sufficiently reduced (>20/10 mm Hg reduction or <140/90 mm Hg). The ABPM device was programmed to record every 30 min between 0600 and 2100 h (daytime) and every 60 min between 2100 and 0600 h (nighttime). Physical activity was monitored electronically by an Activetracer (GMS, Tokyo, Japan), which is a commercially available lightweight and matchbox-sized piezo sensor.10 The device, which was attached to the patient’s waist, was programmed to count each acceleration of more than 0.05 g per 0.1 min as 1. The body motion count was recorded for each minute throughout the measurement period. The mean value of 3 min of Activetracer counts just before BP measurement was defined as the physical activity at that time.10 The patients also reported their activities by filling out questionnaires. Linear regression analysis was used to calculate the correlation (r) and regression (y = ax + b) between BP as well as pulse rate and physical activity, for each subject. “a” from the regression was defined as the degree of BP or pulse rate change caused by physical activity, and “b” was defined as basal BP or pulse rate dependent on physical activity. We also calculated the coefficient of determination as the contribution of physical activity to BP and pulse rate variability.

**Study 2**

Sixteen patients (nine men, seven women) with essential hypertension were enrolled in this study. The mean age of these patients was 55.6 ± 6.5 (range, 48 to 64) years. Informed consent was obtained from all subjects.

An ABPM system and an Activetracer were fitted simultaneously to these patients before (placebo) and after 6 weeks of crossover treatment with nifedipine, 30 to 60 mg/day, as well as benidipine, 2 to 8 mg/day. Linear regression analysis was used to calculate the correlation (r) between BP and physical activity for each patient. The lowest BP measured by ABPM (daytime and nighttime) was compared between the nifedipine and benidipine groups. The evaluation of autonomic nervous activity was performed using an Activetracer, which also measured the R-R interval from an ordinary ECG when attached to chest leads. The data were analyzed by a personal computer using Memcalc.13 The low-frequency/high-frequency ratio (LF/HF, ms²/Hz) was used as the sympathetic nervous activity, and the high-frequency level (HF, ms²/Hz) was used as the parasympathetic nervous activity. Epinephrine (E, ng/mL), norepinephrine (NE, ng/mL), dopamine (DA, ng/mL), and plasma renin activity (PRA, ng/mL/h) were measured before and after nifedipine and benidipine. These hormones were sampled at 1400 h in all patients.

The significance (P < .05) of the studies was determined by using Student’s t test, an ANOVA test, and the χ² test when necessary.

**Results**

**Study 1**

The mean dose of benidipine was 5.4 ± 2.0 mg (range, 2 to 8 mg). According to the questionnaires, all subjects were active in the daytime and slept at nighttime. Both SBP and diastolic blood pressures (DBP) were significantly lower after treatment during the 24-h period (148 ± 8 vs 137 ± 12 mm Hg, 91 ± 10 vs 85 ± 10 mm Hg). However, the pulse rate was not (71 ± 11 vs 71 ± 9 beats/min). SBP was significantly related to physical activity in both the pretreatment and posttreatment periods in all subjects (27/27, r = 0.509 ± 0.124 vs 27/27, r = 0.480 ± 0.119). No significant difference was found between the pretreatment and posttreatment periods in the SBP correlation coefficient (r) and in the degrees of SBP change caused by physical activity (“a”) (0.074 ± 0.032 vs 0.063 ± 0.024 mm Hg/count, respectively). A significant difference (P < .001), however, was found in the basal SBP dependent on physical activity (“b”) between the pretreatment and posttreatment periods (144 ± 12 vs 130 ± 12 mm Hg, respectively). There was no significant difference between the pretreatment and posttreatment periods in the coefficient of determination for SBP (0.272 ± 0.127 vs 0.243 ± 0.117, respectively). Diastolic blood pressure and pulse rate were significantly related to physical activity in many cases in the pretreatment or posttreatment

**Table 1.** 24-hour BP, epinephrine, norepinephrine, dopamine, PRA, LF/HF ratio, and HF levels among the placebo, nifedipine, and benidipine groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>Benidipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h mean BP</td>
<td>152 ± 12/91 ± 10</td>
<td>134 ± 13/80 ± 6*</td>
<td>141 ± 12/83 ± 9*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>41 ± 32</td>
<td>29 ± 23</td>
<td>32 ± 24</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>372 ± 159</td>
<td>403 ± 136</td>
<td>464 ± 163</td>
</tr>
<tr>
<td>Dopamine</td>
<td>14 ± 7.6</td>
<td>13 ± 7.2</td>
<td>15 ± 6.7</td>
</tr>
<tr>
<td>PRA</td>
<td>0.57 ± 0.59</td>
<td>1.20 ± 1.05*</td>
<td>0.75 ± 0.78</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.49 ± 2.2</td>
<td>3.69 ± 1.8</td>
<td>3.64 ± 2.5</td>
</tr>
<tr>
<td>HF</td>
<td>127.5 ± 83.9</td>
<td>101.6 ± 72.8</td>
<td>150.1 ± 77.8</td>
</tr>
</tbody>
</table>

BP = blood pressure; PRA = plasma renin activity; LF = low-frequency; HF = high-frequency.

* P < .05 compared to placebo.
periods (DBP: 16/27, r = 0.311 ± 0.205; PR: 13/27, r = 0.290 ± 0.258). The “a” of DBP changed from 0.041 ± 0.027 to 0.027 ± 0.020 mm Hg/count (P < .05), and the “a” of the pulse rate changed from 0.023 ± 0.025/count to 0.021 ± 0.048 (ns). Basal DBP dependent on physical activity ranged from 89 ± 10 to 81 ± 11 mm Hg (P < .001), and the basal pulse rate ranged from 69 ± 10 to 69 ± 9 mm Hg (ns). Coefficients of determination for the DBP ranged from 0.190 ± 0.138 to 0.134 ± 0.114 (P < .05), and those for the pulse rate ranged from 0.141 ± 0.120 to 0.150 ± 0.153 (ns).

Study 2

Systolic blood pressure was significantly related to physical activity in all subjects who received placebo (16/16) and benidipine (16/16). However, the relationship between SBP and physical activity in patients receiving nifedipine was lost in four cases (12/16), which was significantly (P < .05) different from the results for the placebo and benidipine groups. The 24-h mean BP in nifedipine and benidipine groups were lower than that in the placebo group (Table 1), but there was not a significant difference between these BP in the nifedipine and benidipine groups. The lowest BP measured by ABPM in the daytime and nighttime were 111/68 and 106/65 in the nifedipine groups and 117/73 and 113/69 in the benidipine groups (P < .05). PRA in the nifedipine group was significantly higher than that in the placebo and benidipine groups (1.2 ± 0.57 v 0.75). There were no differences in E, NE, DA, LF/HF, and HF among the three groups (Table 1). Thus, there was a strong relationship between SBP and physical activity in subjects who received placebo and benidipine, but not in subjects who received nifedipine (Fig. 1).

Discussion

A previous study showed that physical activity contributed to about one-quarter of the change in BP. However, there has been little study on the relationship between BP and physical activity, as physical activity is diverse and very difficult to measure quantitatively. In Study 1, we used a piezo sensor that translates physical activity into digits. Another important issue was the number of minutes just before BP measurement that should be considered as the interval in which physical activity affects BP. There have been only a few studies that have dealt with this issue. According to the results of our previous study, a 3-min interval just before BP measurement showed the best correlation between physical activity and BP. Therefore, a 3-min interval was used as the period for estimation of physical activity in the present study.

There are no available data on the effects of antihypertensive agents on ambulatory BP during daily physical activity. In Study 1, SBP was found to be significantly related to physical activity in all subjects in both the pretreatment and posttreatment groups. Diastolic blood pressure and pulse rate were also found to be significantly correlated to physical activity in many subjects during the pretreatment or posttreatment period. This study showed that physical activity contributed to about one-quarter of the changes in BP in a hypertensive state or in a reduced BP state by benidipine. Therefore, physical activity is considered to be an important factor for the evaluation of BP in both an untreated and treated state.

Hypertension is considered to be a disease in which BP is set high. It is not considered to be a disease of BP regulation, although baroreflex sensitivity is reduced. When evaluating the effects of drugs on BP modified by physical activity, we considered two factors to be important. One is the degree of BP change caused by physical
activity ("a") and the other is the basal BP dependent on physical activity ("b"). The reduction in elevated basal BP dependent on physical activity found in the present study suggests normalization of abnormal basal BP.

Maintaining BP to a certain level is essential for humans. For this purpose there are cardiovascular reflexes, by which a number of external stimuli are buffered. Reduction of BP by drugs is one of the external ones. However, nifedipine destroyed the relationship between SBP and physical activity in some subjects in Study 2, though this relationship was maintained during placebo and benidipine administration. This means that nifedipine worked for a short period, during which the reduction of BP was too much to overcome the compensatory mechanism. It was also thought that this agent reduced perfusion pressure to the myocardium during a certain period more than did benidipine, even though the 24-h BP were the same. Some reports have stated that nifedipine is associated with a dose-related increase in mortality in patients with coronary heart disease and state that excessive BP reduction and sympathetic nervous stimulation by nifedipine were partially involved.1,2 In Study 2, nifedipine reduced the lowest BP in 24-h BP monitoring in the daytime and nighttime more than did benidipine, and nifedipine increased the PRA level more than did placebo and benidipine. However, there were no differences in E, NE, DA, LF/HF, and HF levels in the placebo, nifedipine, and benidipine groups. This means that our dose of nifedipine increases PRA without sympathetic nervous stimulation. Some reports have stated that a high renin profile is associated with the subsequent risk of myocardial infarction in spite of the same BP level.15 This report suggested that PRA acts on the direct pathologic effects of excess angiotensin on vascular and myocardial tissue. In this respect, the increase in PRA in Study 2 might be another reason for the increase in cardiac events with nifedipine.

In conclusion, benidipine reduced the elevated basal BP in hypertensive patients without any modification of the relationship between SBP and physical activity. Nifedipine destroyed this relationship. Although the doses of nifedipine used in this study did not influence the sympathetic nervous system, PRA was increased by nifedipine. However, benidipine did not have such effects. These findings indicate that nifedipine might interfere with the adaptation mechanism of BP changed by physical activity and that the activated renin-angiotensin system might cause cardiac events.

References