Rest and Effort Hemodynamic Responses During Prolonged Treatment With Felodipine, 24-h Blood Pressure Monitoring, and Echocardiographic Changes

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In an open study, 16 patients with moderate essential hypertension were treated with 5 or 10 mg felodipine daily for 3 months. Hemodynamic (HD) indices were assessed at rest and during isometric effort (IE) at days 0, 3 to 7, 30, 60, and 90. Treatment efficacy was evaluated by ambulatory blood pressure monitoring for (ABPM) 24 h and divided between awake and sleep periods. Left ventricular mass (LVM) was determined before and at the end of treatment. Treatment normalized blood pressure (BP) in all patients (5 mg in 7 and 10 mg in 9). Systolic diastolic and mean arterial pressure (MAP) decreased significantly during the study \( (P < .01) \). The decrease in BP was significant on day 3 to 7 \( (P < .01) \) and tended to decrease further with treatment. Resting heart rate (HR) did not change. After 3 months systolic and diastolic pressure and MAP decreased significantly. Mean HR during ABPM differed between awake and sleep hours but did not change with treatment. When ABPM was divided into daytime and nighttime the awake BP decreased after 3 months \( (P < .01) \), but sleep measurements showed only a borderline decrease \( (P = .05) \). MAP after 3 months decreased in both awake and sleep periods. LV maximal and minimal dimensions did not change during treatment. Interventricular septum, posterior wall thickness, LVM, LVM/body surface area, and LVM/height tended to decrease, however this change was not significant. Hemodynamic measurements were measured at rest, at peak IE and posteffort. During treatment rest systemic vascular resistance (SVR) and MAP decreased, and there was no difference in ventricular ejection time, HR, and cardiac index. The increase in BP at IE was not prevented by treatment. After effort MAP decreased significantly and SVR tended to decrease in treated patients. Felodipine normalized resting BP in all patients. The main antihypertensive effect came at daytime and was less during sleep. No reflex tachycardia was seen during treatment. Echocardiographic measurements showed preservation of systolic and diastolic function and a tendency of decrease in LVM. Probably longer period of treatment is needed for clear-cut regression of LVM. Felodipine did not prevent the increase in BP and SVR during isometric effort, implying that normal cardiovascular reflexes are preserved during treatment. Am J Hypertens 1997;10:905–912 © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Hemodynamics, felodipine, 24-h blood pressure, echocardiography.
Because the basic derangement in essential hypertension is increased peripheral resistance, the logical approach to optimal treatment should be induction of arterial vasodilatation. Many of the classical arterial vasodilators limit their use due to sympathetic activation, reflex tachycardia, sodium, and water retention. Felodipine is among the new calcium antagonists that cause arterial vasodilatation with gradual effect and less cardiac activation or fluid retention.\(^1,2\) Felodipine is a 1,4-dihydropyridine calcium antagonist with specific activity on vascular smooth muscle cells, which reduces smooth muscle contractility especially in the arterial resistance vessels.\(^2\) In contrast to several other calcium channel blockers, it has been shown that felodipine is devoid of negative inotropic\(^3\) and chronotrophic\(^4,5\) effects, and in contrast to many vasodilators it has natriuretic and diuretic effects.\(^6,7\)

We evaluated the acute and chronic hemodynamic (HD) changes that occur at various stages of prolonged treatment with felodipine at rest and during isometric effort. We used the noninvasive impedance cardiography (IC) method for determining HD parameters.\(^8\) We assessed the efficacy of once daily treatment with felodipine on clinic blood pressure (BP) measurements and on 24-h ambulatory blood pressure monitoring (ABPM), comparing awake and sleep BP before and after treatment. We also compared echocardiographic changes before and at the end of the 3-month treatment period to determine whether decrease in hypertrophy can be seen within this relatively short period of treatment and whether systolic and diastolic function is affected by this specific calcium channel blocker.

**METHODS**

In an open study 16 patients (12 men, 4 women) aged 31 to 67 (mean 52 ± 11) years, with mild-to-moderate uncomplicated essential hypertension underwent a washout period of at least 1 week. Patients treated previously with beta blockers or clonidine were taken off medications for 2 weeks. Patients chosen to participate in the study underwent complete anamnesis, physical examination, routine blood and urine evaluation, electrocardiogram, and chest X-ray. Secondary hypertension was excluded by routine procedures. Heart rate and systolic and diastolic blood pressures were evaluated twice after the patient had rested in the sitting position for at least 10 min. Blood pressure was measured on the same arm on each occasion.

Patients were eligible to enter the study if their diastolic blood pressure at the end of washout period was between 95 and 114 mm Hg. Patients were excluded if there was evidence of secondary hypertension, significant end organ damage, or history of myocardial infarction or cerebrovascular accident 12 months before the study. Patients were excluded if they required medical treatment that might affect their blood pressure or had serious psychiatric or concurrent illness or showed evidence of drug or alcohol abuse or were women of child-bearing potential without sufficient contraceptive measures.

**Study Protocol** After washout the patients underwent ambulatory blood pressure monitoring (ABPM) and echocardiographic examination. Baseline and effort hemodynamic indices were measured and treatment with felodipine was started. The patients received 5 mg felodipine once daily between 9 and 11 AM, they were examined after 3 to 7 days of active treatment and then every 2 to 4 weeks or as needed for 3 months. Felodipine dose was increased to 10 mg once daily if the diastolic blood pressure was above 90 mm Hg.

Blood pressure and heart disease (HD) measurements at rest and peak effort of standardized isometric tests were performed between 8 and 11 AM, before administration of the next dose of felodipine. The measurements were performed on days 0, 3 to 7, 30, 60, and 90 of the study. Echocardiographic measurements and ABPM were performed at the end of the washout period before active treatment and after 90 days of treatment.

**Control Groups** Each patient served as a control of himself or herself at various stages of the study. No placebo group was used in our study as we and our Helsinki committee did not consider it ethical to follow up a group of hypertensive patients without treatment for 3 months. In preliminary experiments we have shown that repetitive pressure on the handgrip device and BP measurement does not cause habituation.

**Experimental Procedures**

**Isometric Handgrip Test** Isometric effort was performed as described elsewhere.\(^9\) Briefly, each volunteer was instructed to press the standard calibrated handgrip device (Dynamometer, Harvard Apparatus, Clifton, NJ) three times at maximal strength. Effort hemodynamic measurements were performed after pressing at one third of the mean strength of three maximal efforts for 90 sec. BP and full HD evaluation were measured at 90 sec of effort while the patient still pressed the handgrip device.

**Hemodynamic Measurements** HD studies were performed using the computerized impedance cardiography (IC) technique (Bomed, Medical Manufacturing Ltd., Irvine, CA). The IC method is based on the fact that human tissue offers impedance to high frequency alternating current that oscillates between thoracic electrodes. The electrical impedance can be detected by sensing electrodes attached above and below heart
level. Because blood conducts the electrical signal, the magnitude of the change in transthoracic impedance depends on the cardiac stroke volume. To estimate cardiac ejection without the thoracic outflow component, the maximal change in impedance at early stage of the systole is used because thoracic outflow is minimal at this time. Because transthoracic electrical impedance is influenced by body position, all measurements were performed at the supine position. Patients with deformation of the chest and pulmonary and valvular disease were excluded from the study. To eliminate changes induced by inspiratory/expiratory variation, the study was performed at supine rest during normal breathing and mean values of 16 cardiac beats were calculated in all measurements. HD measurements were performed after at least 10 min of supine rest and after 90 sec of isometric effort (IE).

The following hemodynamic parameters were measured or calculated using the IC method: ventricular ejection time (VET, sec), heart rate (HR, beats/min), cardiac output (CO, L/min), cardiac index (CI, L/min/m²), mean arterial pressure (MAP, mm Hg), and systemic vascular resistance (SVR, [dyne, sec/cm²]).

ABPM Monitoring was performed using Accu-tracker II (Suntech, Medical Instrumentation, Raleigh NC). BP was recorded at 20 min intervals during awake hours (06:00 to midnight) and at 30-min intervals during sleep hours (midnight to 06:00). Mean ABPM values were calculated for each hour and for awake and sleep periods.

Left Ventricular Mass LVM indices were calculated from echocardiographic data.¹⁰

Blood Pressure Load BP load was calculated as the area under the curve above or below the upper limit of normal on the BP curve, calculated in 1-h units.

Statistical Methods In data analysis we used the paired t test and the nonparametric Signed Rank Test, testing paired difference between baseline assessments and all the postbaseline assessments for quantitative parameters. All tests applied were two-tailed, and P values of 5% or less was considered statistically significant. The data were analyzed using SAS software (SAS Inc., Cory, NC).

RESULTS

All 16 patients had their blood pressure normalized during treatment with felodipine once daily as a single medication. The final dose for normalized blood pressure was 5 mg in 7 patients and 10 mg in 9 patients.

Clinic Blood Pressure Clinic systolic, diastolic, and mean BP decreased significantly during the study. The decrease in systolic blood pressure was by 6.7, 10, 11, and 13% and in diastolic blood pressure by 9, 12, 14 and 15% during the study (Figure 1A). Clinic heart rate measurements at rest, did not change throughout the study, it was 72 ± 10, 74 ± 9, 76 ± 9, 75 ± 8, and 72 ± 10 (mean ± SD) beats/min on days 0, 3 to 7, 30, 60, and 90 of treatment correspondingly.

ABPM Monitoring When pretreatment ABPM data, calculated as the mean of hourly intervals, were compared with measurements performed after 3 months of treatment, systolic, diastolic, and mean arterial pressure were significantly lower after treatment with felodipine (Figure 2).

When 24-h ambulatory blood pressure monitoring was divided between waking (06:00 to midnight), and sleep (midnight to 06:00) measurements, a significant decrease during the day was found after 3 months of treatment, whereas sleep measurements showed a decrease that was of borderline or of no significance. The decrease in mean arterial pressure after 3 months of treatment was significant in both waking and sleep periods (Figure 1B). The mean systolic load, calculated as the area under the curve above or below the normal range, during waking hours decreased from 10.1 to −1 (P = .000), and during sleep hours from 17.6 to −9.4 (P = .025), (Table 1). The mean waking diastolic load decreased from 3.7 to −5.1 (P = .000) and the mean sleep diastolic load decreased from 3.4 to −2.2 (P = .035) (Table 1). Although blood pressure levels decreased significantly after treatment, the circadian rhythm of blood pressure did not change and remained stable.

Mean heart rate, calculated as mean of hourly intervals, during ABPM did not differ before and after 3 months of treatment. Generally mean values during activity hours (08:00 to midnight) were in the range of 75 to 85 beats/min and during nighttime (midnight to 06:00) decreased to the range of 60 to 70 beats/min. Treatment with felodipine did not induce any change in heart rate in 24 ABPM measurements, or when separated to waking and sleep periods. When calculated in mean hourly intervals the heart rate during waking hours (06:00 to midnight) was 77 ± 10 before and 78 ± 12 (beats/min, mean ± SD) after treatment. During sleep hours (midnight to 06:00) the heart rate was 64 ± 9 before and 65 ± 8 after treatment.

Echocardiographic Measurements Left ventricular maximal and minimal dimensions during diastole and systole did not change during the treatment period (Table 2). The thickness of interventricular septum tended to decrease from 11.71 to 10.50 mm, but the decrease was of borderline significance (P = .06). The thickness of the posterior wall of the left ventricle tended to decrease from 10.64 to 10.08 mm, but the decrease was of no statistical significance (P = .2), (Table 2). Left ventricular mass (P = .2), LVM/body
surface area (BSA) decreased from 9.8 to 9.1 (P = .2) and LVM/height also showed a nonsignificant tendency to decrease from 1140 to 1059 (P = .18) (Figure 3).

**Hemodynamic Measurements** Measurements performed at rest, at peak effort of the isometric test, and 1 to 2 min posteffort showed no difference in ventricular ejection time, when pre- and posttreatment values were compared (Table 3). Heart rate and cardiac index were higher at peak isometric effort than at baseline or 1 to 2 min postisometric effort and they did not decrease throughout treatment.

Systemic vascular resistance and mean arterial pressure decreased significantly during treatment with felodipine in measurements performed at rest. During isometric effort systemic vascular resistance index

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**FIGURE 1.** Systolic, diastolic, and mean arterial pressure (mm Hg), during treatment with felodipine 5 or 10 mg once daily as needed at various stages of treatment. A: Clinic blood pressure measurements during treatment with felodipine (in all experiments P < .05 v baseline). B: ABPM measurements, systolic, diastolic, and mean arterial pressure (mm Hg), divided to waking (06:00 to midnight) hours, and sleep (midnight to 06:00) hours before and after 90 days of treatment with felodipine. (P denotes post v pretreatment significance).
FIGURE 2. Mean values of blood pressure measurements (systolic, diastolic, and MAP), during 24-h ABPM. Mean data were calculated for 1-h intervals, pre- and posttreatment values plotted.
(SVRI) and MAP increase at peak effort and decrease to levels close to baseline within 1 to 2 minutes post-effort release. However, at peak effort of isometric test SVRI and MAP did not decrease despite treatment. One to 2 min postisometric effort SVRI and MAP were lower than at peak effort. MAP 1 to 2 min after effort tended to decrease further throughout the treatment period; this decrease was of borderline significance (P < 0.05). SVRI measured 1 to 2 minutes postisometric effort did not change during the study period (Figure 4).

It should be noted that SVRI and MAP increased significantly during peak effort in comparison to rest measurements. Generally, measurements performed 1 to 2 min after isometric effort were similar to measurements at rest.

Adverse Events The following mild adverse events were reported throughout the study: headache, 3 patients; facial flushing, 1 patient; mild edema of legs, 2 patients. Weakness, constipation, diarrhea, and heartburn were reported by 1 patient each. No serious adverse events were reported, and those that were reported were transient, except mild leg edema, which did not justify discontinuation of treatment.

No change in complete blood count and full biochemistry blood tests (bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, uric acid, Na, K, creatinine, cholesterol, triglycerides) was seen.

DISCUSSION

Prolonged treatment with felodipine decreased blood pressure efficiently and without significant side effects. The decrease in blood pressure was evident already on the first visit after beginning of treatment, ie, within 3 to 7 days and a tendency to decrease further was seen with continuation of the study (Figure 1A). Blood pressure reached the goal levels of less than 140/90 mm Hg in all 16 patients with single drug treatment of 5 or 10 mg of felodipine once daily. The decrease in blood pressure was not accompanied by reflex tachycardia and no significant change in heart rate was seen. These findings were seen both in clinic blood pressure measurements and with 24-h ambulatory blood pressure monitoring.

The circadian rhythm of 24-h blood pressure measurements did not change with felodipine treatment and the nocturnal dip was preserved with a proportional decrease throughout 24-h measurements (Figure 2). When ABPM recordings were divided to waking and sleep hours and the relative blood pressure load was calculated, the systolic blood pressure decreased significantly during waking hours (Figure 1B). However, during sleep hours the systolic blood pressure decreased only slightly with borderline significance (P < 0.05) and diastolic blood pressure did not decrease significantly (P = 0.109). Obviously in our experiment sleep time represents the end of effect of the previous dose and it may represent a somewhat lesser trough effect. It has been shown that the trough to peak ratio for felodipine in its extended release formulation was 0.6711; however, in another study it was shown that after correction for placebo effect the

### TABLE 1. MEAN BLOOD PRESSURE LOAD, CALCULATED BY HourLY INTERVALS DURING TREATMENT WITH FELODIPINE

<table>
<thead>
<tr>
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<th>Before Treatment</th>
<th>After Treatment</th>
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<tbody>
<tr>
<td>Systolic</td>
<td></td>
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<tr>
<td>06:00–midnight</td>
<td>10.1 ± 12.7</td>
<td>−1.0 ± 13.7</td>
</tr>
<tr>
<td>Midnight–06:00</td>
<td>17.6 ± 16.1</td>
<td>9.4 ± 13.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06:00–midnight</td>
<td>3.7 ± 5.7</td>
<td>−5.1 ± 7.3</td>
</tr>
<tr>
<td>Midnight–06:00</td>
<td>3.4 ± 6.8</td>
<td>−2.2 ± 5.7</td>
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### TABLE 2. ECHOCARDIOGRAPHIC DATA BEFORE AND AFTER 3 MONTHS OF TREATMENT WITH FELODIPINE 5 OR 10 MG AS NEEDED (MILLIMETERS)

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
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<tbody>
<tr>
<td>Interventricular septum</td>
<td>11.71 ± 1.90</td>
<td>10.50 ± 1.22</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>10.64 ± 1.34</td>
<td>10.08 ± 1.12</td>
</tr>
<tr>
<td>Maximal LV dimension</td>
<td>48.00 ± 5.22</td>
<td>47.75 ± 5.21</td>
</tr>
<tr>
<td>Minimal LV dimension</td>
<td>27.13 ± 5.49</td>
<td>28.20 ± 5.40</td>
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LV: left ventricular.
calculated trough to peak ratio was less than 0.50. Alternatively, the lack of excessive blood pressure decrease during sleep hours may be of advantage because sleep blood pressure was normalized despite the somewhat lower decrease in blood pressure. This effect may be of advantage in patients with atherosclerosis and impaired tissue perfusion, especially in patients with progressive impairment of cerebral vessels in which an excessive decrease in blood pressure may be detrimental. Treatment with felodipine was not associated with reflex tachycardia in the acute and chronic stages of follow-up at clinic measurements and during ABPM. Heart rate did not change during awake and sleep periods although it was significantly lower during sleep period. Heart rate tended to increase slightly during treatment but no significant change was seen at rest, at peak isometric effort, and 1 to 2 min posteffort at various steps of treatment with felodipine (Table 3).

Treatment with felodipine for 3 months did not show any negative inotropic effect. Echocardiographically, no change in left ventricular systolic and diastolic dimensions was found. While we performed noninvasive hemodynamic measurements we found no change in cardiac index during treatment with felodipine at rest, at peak effort of isometric test, and 1 to 2 min after effort. Similarly, echocardiographic data did not show any decline in ventricular systolic

<table>
<thead>
<tr>
<th>TABLE 3. HEMODYNAMIC DATA AT REST, PEAK ISOMETRIC EFFORT AND 1 TO 2 min POSTEFFORT AFTER 3-MONTH TREATMENT WITH FELODIPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular ejection time (msec)</strong></td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
</tr>
<tr>
<td>Rest</td>
</tr>
<tr>
<td>Peak IE</td>
</tr>
<tr>
<td>Post IE</td>
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<tr>
<td><strong>Heart rate (beats/min)</strong></td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
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<tr>
<td>Rest</td>
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<tr>
<td>Peak IE</td>
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<td>Post IE</td>
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</tbody>
</table>

IE: inspiratory/expiratory.

FIGURE 4. Hemodynamic parameters—cardiac index, MAP, SVR—at various stages of treatment with felodipine, 5 or 10 mg as needed, measured at rest, peak isometric effort, and 1 to 2 min postisometric effort.
and diastolic dimensions (Table 2). These results comply with previous studies, which confirm that treatment with felodipine is devoid of negative inotropic effect. Treatment with felodipine did not prevent the blood pressure and SVRI increase in response to isometric effort (Figure 4). This phenomenon implies that treatment with felodipine will preserve the normal cardiovascular responses to effort but will not prevent the excessive increase in blood pressure during isometric effort. This phenomenon may be of advantage in preserving cardiovascular reflexes, which is especially important in patients with progressive arterial disease.

It has been shown that treatment with felodipine is associated with decrease in the LVM index. In another study that included 52 patients in the felodipine group treated for 8 weeks, the absolute changes in LVMI were small or absent. In another study felodipine and the combination of felodipine and metoprolol reduced LV hypertrophy to the same extent when the blood pressure was reduced to the same extent. In our study, because of the need to perform hemodynamic measurements, a smaller group of 16 patients was treated. We found that treatment with felodipine was accompanied by a tendency of decrease in interventricular septal thickness, although the decrease was not statistically significant (P = .06). No change in posterior wall thickness and in calculated left ventricular mass was seen. Similarly no change was seen in ventricular ejection time at various stages of treatment, at peak effort of isometric test, and at 1 to 2 minutes posteffort (Table 3). Our findings of the tendency to decrease myocardial wall thickness as a manifestation of regression of LVH, without definite statistical significance, is probably due to the fact that a relatively small group of patients was treated for relatively short period of time.

REFERENCES