The effects of felodipine on cardiac hemodynamics in primary hypertension

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Calcium antagonists, like many other antihypertensive agents, have regressive effect on left ventricular hypertrophy, which often accompanies systemic hypertension. In this study, the effect of felodipine on cardiac hemodynamics and left ventricular mass in hypertensive patients was investigated. The study group included 17 primary hypertensive subjects, whose mean sistolic and diastolic blood pressure values were 156±3/103±1 mmHg. The subjects were given felodipine 5 mg daily after two weeks' duration of placebo period; the dose was doubled if diastolic blood pressure was not lower than 90 mmHg after two weeks, and metoprolol 100 mg daily was added, if it was still equal or higher than 90 mmHg while on 10 mg felodipine. After 6 weeks' duration of felodipine treatment, the response rate was 88%, with 7.5 mg daily mean dose of felodipine. After 6 weeks' duration of felodipine treatment, endsistolic posterior wall thickness increased and endsistolic stress decreased; both representing improvement in systolic function of left ventricule. A slight decrease in left ventricular mass was observed. Thus, it is suggested that, in addition to effective antihypertensive effect, felodipine may be beneficial for the improvement of the left ventricular functions. [Turk J Med Res 1992; 10(5):267-271]

Key Words: Felodipine, Hypertension, Hemodynamics

Calcium antagonists (CA) are being used increasingly in the first step treatment of hypertension, in recent years (1-3). In addition to effective lowering of blood pressure, CA's are df benefit on coronary circulation (4) and myocardial structural changes (5,6) which accompany hypertension.

Left ventricular hypertrophy, which is the result of hemodynamic alterations caused by systemic hypertension, increases cardiovascular morbidity and mortality independent from increased blood pressure, coronary artery disease and heart failure (7,8). The risk of mortality may be diminished by means of regression of left ventricular mass (9). Some antihypertensive agents, including CA's, have ability to diminish the increased left ventricular mass (10,11).

CA's exert their action via the inhibition of the entry of calcium into vascular smooth muscle and myocardial cells. It is well known that there are significant differences between CA's according to vascular or cardiac selectivity. Higher the vascular/cardiac selectivity ratio, lesser the effect on the contraction and impulse generation and conduction of the heart. This ratio is 1, 7 and 14 for verapamil, diltiazem and nifedipine, respectively. The highest vascular selectivity belongs to felodipine amongst CA's, with vascular/cardiac selectivity ratio of 118 (12).

In the present study, the effects of felodipine on cardie hemodynamics and left ventricular mass in mild to moderate hypertensive patients were investigated.

PATIENTS AND METHODS

The subject in the study group were selected from the primary hypertensive patients referring to Cardiology Department, Hacettepe University Medical School, whose diastolic blood pressure (DBP), which was measured at three different occasions, following 10 minutes' rest in supine position, was between 95 and 110 mmHg, age between 25 and 70 years, and who had no antihypertensive medication during the previous four weeks. The subjects whose, liver transaminase levels higher than twice the upper normal range, glomerular filtration rate less than 30 ml/min, and who were pregnant or breast-feeding were excluded.

The study group included 17 subjects (12 women, 5 men; mean age 47.4±2.4 years, mean height 160.0±1.9 cm, mean weight 78.1 ±2.9 kg, mean body surface area 1.79±0.03 m).

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The study period was 8 weeks. The subjects were called for visit every two weeks on an out-patient basis. Following the first two weeks -the placebo period-, oral felodipine 5 mg daily was started; the dose was doubled if DBP was higher than 90 mmHg at the fourth week visit and oral metoprolol 100 mg daily was added if DBP was still higher than 90 mmHg at the sixth week visit. The study ended at the eighth week.

Blood pressure measurements were performed by the same physician (0.6.) by mercury sphygmomanometer from both arms, 10 minutes after resting in supine position and 5 minutes after standing. DBP value was assigned to Korotkoff phase V.

Biochemical analysis of blood (by Dacos Coulter Electronics Inc. Discrete Analyzer, Florida, U.S.), serum lipids, complete blood count (by Coulter Counter Model S-plus-IV, Luton, England) and electrocardiographical (ECG) analysis (by three-channel Hewlett-Packard instrument, speed 50 mm/sec, amplitude 1 mV/10 mm) were performed before and after placebo period and at the second and sixth week of felodipine treatment.

Echocardiographical (ECHO) assessments of the subjects were done by Toshiba Sonolayer SSH-60, before and after the placebo period and at the end of the study, at about 11:00 AM, three hours after the dosing. M-mode and two- dimensional records were obtained via 1 cm diameter, 2.25 MHz transducer, together with simultaneous ECG recordings. Diastolic parameters were measured just at the beginning of QRS complexes. Cavity and wall measurement were obtained from the cross-section just beneath the mitral valve, at corda tendinea level. All ECHO images were recorded onto videotapes and reassessed at the end of the study. Following formulae were used for the estimation of the ECHO data:

$$\log BSA = (0.425 \times \log W) + (0.725 \times \log H) - 0.1436 \quad (13)$$

$$\text{Volume (ml)} = \frac{7}{2.4 + \text{Diameter}} \times \text{Diameter}^3 \quad (14)$$

$$\text{Fractional shortening (FS) (\%)} = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDV}} \times 100 \quad (15)$$

$$\text{Ejection fraction (EF) (\%)} = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}} \times 100$$

$$\text{Stroke volume (SV) (ml)} = \text{LVEDV} - \text{LVESV}$$

$$\text{Stroke index (SI) (ml/m}^2\text{)} = \frac{\text{Stroke volume}}{\text{BSA}}$$

$$\text{Cardiac output (CO) (L/min)} = \text{Stroke volume} \times \text{Heart rate}$$

$$\text{Cardiac index (CI) (L/min/m}^2\text{)} = \frac{\text{Cardiac output}}{\text{BSA}}$$

$$\text{Total peripheral resistance (TPR) (dyn.sec.cm}^{-5}\text{)} = \frac{\text{mean BP}}{\text{Cardiac output}} \times 80$$

$$\text{Endostolic stress (ESS) (mmHg)} = \frac{0.334 \times \text{LVESD} \times \text{Systolic BP}}{\text{ESPWT} \times \left[1 + \frac{\text{ESPWT}}{\text{LVESD}}\right]} \quad (16)$$

$$\text{Left ventricular mass (VM) (gr)} = 1.04 \times [(\text{LVEDD} + \text{EDST} + \text{EDPWT})^3 - \text{LVEDD}^3] - 13.6 \quad (17)$$

$$\text{Left ventricular mass index (VMI) (gr/m}^2\text{)} = \frac{\text{Ventricular mass}}{\text{BSA}}$$

The abbreviations in these equations are as follows:

BSA	Body surface area, in m ,
W	Weight, in kg.,
H	Height, in cm.,
LVEDD	Left ventricular enddiastolic diameter, in mm.,
LVESD	Left ventricular endsistolic diameter, in mm.,
LVEDV	Left ventricular enddiastolic volume, in mm³,
VESV	Left ventricular endsistolic volume, in mm³,
BP	Blood pressure, in mmHg,
ESPWT	Endsistolic posterior wall thickness, in mm.,
EDST	Enddiastolic septal thickness, in mm.

Student's t-test for paired samples were applied for the comparison between parameters obtained before and after placebo and drug.

RESULTS

Initial resting mean SBP and DBP values were 156±3 and 103±1 mmHg, respectively. Whilst these values didn't show any change after the placebo period, 4.5% and 6.0% decrements were observed in mean SBP and DBP, respectively, following two weeks' duration of 5 mg/day felodipine treatment. The response rate, which was described as "DBP lower than 90 mmHg" was 59% (10 of 17 subjects). The dose of felodipine in the remainders was doubled. At the sixth week, one patients was withdrawn from the study, because the drug had to be stopped due to severe headache while on 10 mg/day felodipine regimen. At the end of the study, mean decrements in SBP and DBP were 8.0% and 14.0%, respectively. The response rate was 88%. Standing SBP and DBP exhibited declines parallel to supine measurements. Orthostatic hypotension was not observed in any patient. Mean felodipine doses were 5, 7.1 and 7.5 mg/day during the second, third and fourth two weeks' periods, respectively (Table 1).

Table 1. Supine and standing systolic, diastolic and mean blood pressure and heart rate values during the study

	Before	After Plaacebo	2. week	4. week Treatment	6. week
Supine					
SBP(mmHg)	156±4	156±4	149±4	144±4	140±2"
DBP(mmHg)	103±1	101+2	95±2	87±2	88±2***
MBP (mmHg)	121 ±2	120±3	11313	107±3	105±1**
HR (/min)	74+3	76±2	73+2	75±3	74+2
Standing					
SBP (mmHg)	149±5	150+5	143±4	136±5	133±3*"
DBP (mmHg)	99±3	99±3	92+3	84±3	83±2*"
MBP (mmHg)	116±3	116±3	110±3	101 ±3	100±2"*
HR (/min)	81+3	80±2	78±1	79±3	77±2

SBP: Systolic blood pressure, DBP: Diastolic blood pressure,, MBP: Mean blood pressure, HR: Heart rate
p<0.05," : p<0.01,*" : p<0.001.

Length of PR, QRS and QT intervals and criteria of left ventricular hypertrophy obtained from ECG recordings didn't change during the study period (Table 2).

Following 6 weeks' duration of treatment with felodipine, ESPWT increased form 14.9±0.5 to 16.3±0.3 mm (p<0.001). ESS, which was 74.2±7.9 mmHg at the beginning of felodipine treatment, diminished to 56.6±3.7 mmHg after 6 weeks on felodipine (p<0.01). TPR decreased from 1547±104 to 1441±87 dyn. sec. cm^{-5}. The slight decrement in left ventricular mass was not found to be significant (Table 3).

The biochemical analysis of blood, including renal and liver function tests, blood glucose, electrolytes, urate and serum lipids were all in normal ranges during the study, except creatin phosphokinase, which showed increase from 76±9 IU/L at the beginning of the treatment, to 109±27 IU/L, at the end of the study. White blood cell, red blood cell and platelet counts and hemoglobin and hematocrit values didn't show any alteration during the study.

DISCUSSION

The prevention of the complications has key importance in the management of systemic hypertension. Therefore, in addition to effective lowering of blood pressure, the regression of left ventricular hypertrophy should also be aimed in hypertensive patient.

Table 2. Electrocardiographical values during the study

	Before Placebo	After Placebo	After Felodipine
PR (msn)	141 ±6	145±5	143±4
QRS (msn)	74±3	72+6	75±4
QT (msn)	342±9	351+8	343±6

The prototype of the drugs which have lowering effect on left ventricular mass is methyldopa. CA's, angiotensin-converting-enzyme inhibitors, p-blockers and diuretics have similar effects. On the other hand, treatment of hypertension by direct vasodilators causes increment in left ventricular mass (10,11). More interestingly, it has been demonstrated that methydopa decreased left ventricular mass in normotensive rats, which had not left ventricular hypertrophy; and it has lowering effect even on right ventricular mass both in spontaneously hypertensive rats (SHR) and normotensive rats (7). In the light of all these data, it has been suggested that the effects of antihypertensive drugs on left ventricular mass do not rise solely from the hemodynamic alterations; the direct effects of the drugs on myocardial protein and collagen metabolisms may be dissociated from hemodynamic effects (18). The minimal duration of treatment which is effective on left ventricular mass has usually been observed as 4-6 weeks in animal studies, and 8-12 weeks in human studies.

Although it is a heterogenous group according to structural, pharmacological and hemodynamic properties, the effects of CA's on left ventricular mass show similarity. It is well known that diltiazem (19), verapamil (5), nifedipine (7), nitrendipine (6) and nicardipine (20) regress left ventricular wall thickness and mass in SHR and hypertensive humans.

Felodipine may improve the cardiovascular changes accompanying systemic hypertension. The studies on SHR have shown that felodipine, alone (21) or in combination with metoprolol (22), may regress coronary hypertrophy. In the study on morphometric analysis of coronary resistance vessels in SHR, it is reported that medial thickness of the vessels decreased, medial thickness/diameter ratio was normalized and coronary circulation improved (23). Wetzchewald et al (24) have studied the effects of felodipine alone

Table 3. Echocardiographical parameters during the study

		Before Placebo	After Placebo	After Felodipine
LVEDD	(mm)	46.7+0.9	50.3±1.4	49.9±1.1
LVESD	(mm)	30.6±0.9	30.1 ±1.3	30.2±1.1
EDPWT	(mm)	9.3±0.3	9.50±0.3	9.2±0.4
ESPWT	(mm)	13.9±0.4	14.9±0.5	16.3±0.3"
EDST	(mm)	9.3±0.3	9.2±0.4	8.9±0.3
LVEDV	(ml)	117±5	122±8	119+7
LVESV	(ml)	38±2	37±5	37±3
EF	**(%)**	67.811.6	69.6±2.5	69.5±2.0
FS	**(%)**	38.2±1i»-	40.1 ±2.1	39.611.6
SV	(ml)	79.8±4.0	85.1 ±6.3	82.2±4.4
SI	(ml/m²)	44.8±2.1	46.9±2.9	45.8±2.3
CO	(L/min)	5.9±0.3	6.7±0.5	6.2±0.5
PI UI	*H* **(minima ^L/min/m ¡**	**o q**+n **9**	3.7±0.2	3.5±0.3
TPR	(dyne.sec.cm⁵)	1698+96	1547±104	1441±87
ESS	(mmHg)	80.1 ±4.7	74.2±7.9	56.5±3.7*
VM	(gr)	191 ±9	200±16	187±16
VMI	(gr/m²)	107+5	110±7	104±8

LVEDD: Left ventricular enddiastolic diameter,
LVESD : Left ventricular endsystolic diameter,
EDPWT Enddiastolic posterior wall thickness,
ESPWT Endsystolic posterior wall thickness,
EDST : Enddiastolic septal thickness,
LVEDV: Left ventricular enddiastolic volume,
LVESV : Left ventricular endsystolic volume,
EF Ejection fraction,
FS Fractional shortening,
SV Stroke volume,
SI Stroke index
CO Cardiac output,
CI Cardiac index,
TPR Total peripheral resistance,
ESS Endsystolic stress,
VM Ventricular mass,
VMI Ventricular mass index
*: p<0.01, ": p<0.001

or in combination with metoprolol, on cardiac structure of hypertensive patients whose left venticular posterior walls were thicker than 11.5 mm, by echocardiography assessment. Following 9 months' duration of treatment, it was observed that left ventricular mass decreased from 190 to 170 gr and LVPW and septal thickness measurements from 12.5 to 11.0 mm.

In the present study, it is shown that 6 weeks' duration of treatment of hypertensive patients with oral felodipine has benefical effects on systolic functions of left ventricular myocardium. This is represented by the increased ESPWT and decreased ESS. Slight decrease in ventricular mass did not reach to statistically significant level, probably because 6 weeks are not enough for lowering of ventricular mass, but this led us think hopefully on the regressive effect on left ventricular myocardium of long-term felodipine treatment.

Felodipinin primer hipertansiyonda kardiak hemodinami üzerindeki etkileri

Kalsiyum antagonistlerinin de, bir çok diğer antihipertansif ajan gibi sistemik hipertansiyona eşlik eden sol ventrikül hipertrofisini geriletici etkileri vardır. Bu çalışmada felodipinin hipertansif hastalarda kardiak hemodinami ve sol ventrikül kitlesi üzerine etkileri araştırıldı. Çalışma grubunu ortalama sistollk ve diastolik kan basıncı 156±3/103±1 mm Hg olan 17 primer hipertansif hasta oluşturdu.

Hastalara iki haftalık plasebo dönemini takiben 5 mg/gün felodipin başlandı. İki haftalık tedaviyle diastolik kan basıncı 90 mmHg'nın altına inmeyenlerde doz iki katına çıkıldı; 10 mg/gün felodipin'le diastolik kan basıncı 90 mmHg ve üzerinde devam edenlerde tedaviye 100 mg/gün metoprolol eklendi. Altı hafta süreli felodipin tedavisi sonunda yanıt oranı, ortalama 7.5 mg/gün felodipin'le %88 oldu. Altı hafta sonunda sistolsonu arka duvar kalınlığında artma ve sistol sonu stress'te azalma gözlendi; her iki değişiklik de sol ventrikül sistolik fonksiyonlarında düzelme olduğunu göstermektedir. Sol ventrikül kitlesinde az da olsa azalma saptandı. Sonuç olarak, etkin bir antihipertansif ajan olmasının yanısıra, felodipinin sol ventrikül fonksiyonları açısından da yararlı olabileceği sonucuna varıldı. [Türk Tıp Araştırma 1992; 10(5):267-271]

Anahtar Kelimeler: Felodipin, Hipertansiyon, Hemodinami

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