Effects of Low-Dose Treatment with Felodipine Versus Fosinopril in Chinese Patients with Nonischemic Heart Failure and Normal Blood Pressure: A Double-Blind, Randomized, Crossover Study

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ABSTRACT

Background: Two second-generation calcium channel blockers, felodipine and amlodipine besylate, have been associated with similar high mortality rates in patients with ischemic heart failure (HF) but not in patients with nonischemic causes of HF. In patients with nonischemic HF, amlodipine might have a beneficial effect on survival. However, no difference in mortality rates was found between felodipine and placebo in a nonischemic HF group. Felodipine 10 mg/d was used in 1 large study, a dose considered high for nonischemic HF usually associated with normal blood pressure (BP).

Objective: The aim of this study was to compare the effects of 12-week, low-dose treatment with felodipine versus those of an angiotensin-converting enzyme inhibitor, fosinopril sodium, in patients with nonischemic HF and normal BP.

Methods: This double-blind, randomized, crossover trial was conducted at Taipei Medical University Hospital (Taipei, Taiwan). Patients aged ≥ 18 years with angiographically proved, nonischemic HF and normal BP who were being treated with an optimal regimen of digitalis and diuretics were enrolled. After a 2-week run-in period, patients were randomized to first receive 12 weeks of treatment with felodipine tablets (2.5 mg/d) or fosinopril tablets (7.5 mg/d) and, after a 2-week washout period, were crossed over to the opposite treatment. Efficacy analysis was performed before (baseline) and after treatment and in-

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cluded symptomatic assessment using a 7-grade clinical scale; 2-dimensional echocardiography (2-D echo); exercise tests; and neurohumoral data, including plasma renin activity, plasma aldosterone, and 24-hour urinary epinephrine (E) and norepinephrine (NE) measurements. The primary end point was death due to HF, and the secondary end point was hospital admission due to worsening HF. Compliance was measured using a pill count at the end of each treatment period.

Results: We enrolled 33 patients. One developed worsening HF during the run-in period and was admitted. A total of 32 patients entered the study (18 men, 14 women; mean [SD] age, 48.2 [6.3] years [range, 34–56 years]; mean [SD] systolic BP, 117.2 [9.8] mm Hg [range, 100–138 mm Hg]; mean [SD] diastolic BP, 59.4 [5.7] mm Hg [range, 50–72 mm Hg]). No hospital admission or cardiac death due to HF occurred during 12 weeks of treatment. Twenty-seven patients were included in the felodipine assessment, and 30 patients were included in the fosinopril assessment. Significant improvement in clinical score was noted in both treatment groups (both $P < 0.01$). The clinical scores did not differ significantly between the 2 treatments. No significant differences were found in 2-D echo parameters between treatments or within groups after treatment versus baseline. Significant improvement in exercise duration was noted with both study drugs after treatment versus baseline (both $P < 0.01$). No significant difference in exercise duration was found between the 2 treatments. Urinary E and NE were not significantly different between treatments or after treatment with either study drug compared with baseline.

Conclusion: The present findings suggest that, in Chinese patients with moderate to severe HF who have normal BP and insignificant coronary artery disease and were being treated with diuretics and digitalis, a 12-week, low-dose course of felodipine (2.5 mg/d) as a vasodilator was associated with as satisfactory an outcome as standard treatment with fosinopril (7.5 mg/d). (*Curr Ther Res Clin Exp.* 2004;65:204–221) Copyright © 2004 Excerpta Medica, Inc.

Key words: calcium channel blocker, felodipine, heart failure.

INTRODUCTION

Treatment of heart failure (HF) is one of the most formidable challenges in clinical practice. Vasodilators are now accepted worldwide as an important treatment option in the management of HF.^{1,2} Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve functional status and the prognosis of patients with HF in randomized, controlled trials.^{3,4}

Calcium channel blockers (CCBs), another class of vasodilators, have been approved by the US Food and Drug Administration for the treatment of hypertension and ischemic heart disease,⁵ but have not been widely accepted as a treatment for HF.⁵ First-generation CCBs are associated with adverse effects (AEs) in patients with HF mainly due to their negative inotropic effects and reflex neurohumoral activation.^{6–8} The second-generation CCBs were expected to be beneficial for patients with HF, but studies have shown conflicting

results.^{5,7} Second-generation CCBs appear to be a rational option for the treatment of HF, because up to 70% of patients with HF have ischemia and/or hypertension as the underlying cause.⁵ However, it is not known whether second-generation CCBs are suitable for patients with nonischemic HF and normal blood pressure (BP).

As reported in 2 large trials—the Vasodilator Heart Failure Trial III⁹ (V-HeFT III) and the Prospective Randomized Amlodipine Survival Evaluation¹⁰ (PRAISE)—patients who were randomized to receive second-generation CCBs (felodipine or amlodipine besylate), compared with those who received placebo, had no worsening of HF, but also had no reduction in long-term mortality. Both studies showed similar high mortality rates in patients with ischemic HF. However, a different result was found in patients who had nonischemic causes of HF. A subanalysis¹¹ of the PRAISE study suggested that in patients with nonischemic HF, amlodipine might have a beneficial effect on survival. However, no significant difference in mortality rates was found between felodipine and placebo in the nonischemic HF group in V-HeFT III.⁹ Felodipine 10 mg/d—a dosage considered high for nonischemic HF usually associated with normal BP—was used in V-HeFT III.⁹ Indeed, studies that specifically focus on patients with nonischemic HF and normal BP treated with low-dose felodipine have not been reported, according to a MEDLINE search (key terms, *nonischemic heart failure*, *normal blood pressure*, and *felodipine*; years, 1966–2004).

The aim of this study was to compare the effects, including symptomatic and hemodynamic profiles, of 12-week, low-dose treatment with felodipine versus those of an ACE inhibitor, fosinopril sodium, in patients with nonischemic HF, normal BP, insignificant coronary artery disease, and who were being treated with an optimal regimen of digitalis and diuretics.

PATIENTS AND METHODS

Study Design

This double-blind, randomized, crossover trial was conducted at the Taipei Medical University Hospital (Taipei, Taiwan). The study was approved by the Committee on Human Studies at the hospital and was conducted in accordance with the Declaration of Helsinki and its amendments.

Patients

We enrolled patients aged ≥ 18 years with angiographically proven, nonischemic causes of moderate to severe HF, normal BP, insignificant coronary artery disease, and who were being treated with an optimal regimen of diuretics and digitalis. Eligible patients had a left-ventricular ejection fraction (LVEF) $< 40\%$ and left-ventricular end-diastolic dimension (LVDd) > 55 mm, as measured by one of the investigators (N.C.C.) using 2-dimensional echocardiography (2-D echo), and insignificant coronary artery disease, as assessed using coronary angiography within 1 month before enrollment. We excluded patients who had

a history of diabetes mellitus, thyroid disorder, or neuromuscular disorder. We also excluded patients with hypo- or hypertension (sitting systolic/diastolic BP [SBP/DBP] <100/<50 mm Hg or >140/>90 mm Hg, respectively); evidence of coronary artery disease (coronary artery stenosis >50% in any main coronary artery on either plane of biplane quantitative coronary angiography); valvular stenosis; moderate to severe aortic and mitral valvular regurgitation; specific causes (alcoholic, periportal, and metabolic) of myocardial disease; active myocarditis; constrictive pericarditis; stroke; severe pulmonary, renal, or hepatic disease; a history of cardiac arrest or sustained ventricular tachycardia or fibrillation within 1 year before enrollment; and the inability to exercise >3 minutes. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. Women of childbearing age were required to use an effective method of birth control throughout the study. Other exclusion criteria were fasting plasma glucose level >125 mg/dL, serum creatinine concentration >3.0 mg/dL, serum potassium concentration <3.5 or >5.5 mmol/L, and treatment with class I_C antiarrhythmic agents. All of the patients provided written informed consent to participate.

Methods

The crossover and follow-up process is summarized in the **figure**. All medications except diuretics and digitalis were stopped, and patients were given placebo identical to the study drugs in a single-blind fashion for a 2-week run-in period. The dosages of diuretics and digitalis were individually titrated until optimal response (ie, activities of daily living were improved and no symptoms of toxicity were found) was achieved.

On the first day of the first treatment phase, symptomatic assessment (using a 7-grade clinical score detailed later), 2-D echo data, exercise performance, and neurohumoral profile were acquired. Patients were randomly assigned (using blocks of 2 patients assigned “AB” for digits 0 to 4 and “BA” for digits 5 to 9, using a table of random numbers to ensure equal numbers of patients receiving both treatment regimens) to 12-week oral treatment with felodipine tablets, 2.5 mg/d, or fosinopril tablets, 7.5 mg/d. Both treatments were self-administered orally, once daily, in the morning and were identical in appearance. Because investigating the effects of a low-dose regimen of these drugs was the objective of this study, titration to higher doses was not done. Outpatient visits were scheduled every 2 weeks after randomization for symptomatic assessment.

The day after the first treatment phase, patients were reassessed (symptomatic assessment, 2-D echo data, exercise performance, and neurohumoral profile). On completion of these assessments, patients were given placebo for a 2-week washout period, after which they were reassessed before entering the crossover phase of the trial. At the end of the second 12-week treatment period, patients were reassessed. The assessments were carried out at the same time of day and at the same time after medication in each patient. Treatment compliance was assessed by a nurse using pill counts.

Figure. Study design. ● = baseline of the first treatment; □ = assessment was performed; ▲ = baseline of the second treatment. *One of 33 patients (3.0%) was hospitalized due to worsening heart failure; †1 of these patients withdrew due to ankle edema; ‡1 of these patients withdrew due to intractable night cough; §3 of these patients were withdrawn due to worsening heart failure, poor compliance, or death from ovarian cancer (1 patient each), leaving 12 study completers in the group treated second with felodipine.

The primary end point was death due to HF. The secondary end point was hospital admission due to worsening HF.

Efficacy Assessment

Symptomatic Assessment

At each visit, patients were asked to assess symptomatic changes since the previous visit using a 7-grade scale (1 = markedly worse, 2 = moderately worse, 3 = slightly worse, 4 = unchanged, 5 = slightly improved, 6 = moderately improved, or 7 = markedly improved). Grades were recorded by a nurse. The clinical score based on this scale was recorded on the first day of the first treatment phase before performing exercise tests and was set at 4. At each subsequent visit (every 2 weeks), the score increased or decreased cumulatively, depending on the degree of change from the previous visit.⁷ The baseline clinical scores were recorded on the first day of the first and second treatment phases. The clinical scores at the end of both treatment periods were recorded for comparison.

Echocardiography

We performed 2-D echo on the first day of the first and second treatment phases (baseline data), just prior to the exercise test, using an Ultramark 7

phased-array ultrasound system (Advanced Technology Laboratory, Bothell, Washington) with a 2.5-MHz transducer. The reassessments at the end of both treatments were recorded for comparison. The operator (N.C.C.) recorded 2-D echo images on a videotape recorder. Tapes were analyzed by the operator on a Panasonic editing controller system with an AG-7350 video recorder (Panasonic, Tokyo, Japan). All parameters were calculated using the mean of 5 successive cardiac cycles. Parasternal long-axis 2-D echos were obtained by orientation of the sector plane parallel to the longitudinal axis of the left ventricle. LVDd was the largest LV dimension at end-diastole (R-wave peak of a simultaneously recorded electrocardiogram). Left-ventricular end-systolic dimension (LVDs) showed its shortest dimension at end-systole. We used the following equation to calculate the left-ventricular mass index (LVMI):

$$\text{LVMI (g/m}^2\text{)} = (V_{\text{epi}} - V_{\text{endo}}) \times 1.05/\text{BSA},$$

where V_{epi} = left-ventricular epicardial enclosed volume, V_{endo} = endocardial enclosed volume, and BSA = body surface area. The latter 2 variables were measured at end-diastole and were calculated from the apical 4-chamber (A_1) and 2-chamber (A_2) views by use of the biplane area-length formula:

$$V = 8A_1A_2/3\pi L,$$

where L = the lesser of the lengths of the long axes of these 2 views. We also used the following equations to calculate fractional shortening (FS) and LVEF, respectively:

$$\text{FS} = (\text{LVDd} - \text{LVDs}/\text{LVDd}) \times 100$$

$$\text{LVEF} = (\text{LVDV} - \text{LVS}/\text{LVDV}) \times 100,$$

where LVDV and LVS were V_{endo} measured at end-diastole and end-systole, respectively. The same operator blinded to treatment assignment performed echos throughout the study. A physician blinded to group assignment calculated all echocardiographic parameters off-line.

Intraobserver variations in calculating all parameters of 2 identical echocardiograms were estimated in all patients before and after treatment on 2 occasions, with an interval of 2 months between measurements. Meanwhile, intraobserver variations in measurements between 2 recordings (the data of 3 days before and the first day of the first treatment phase) in the same patient, with an interval of 3 days, were assessed in all patients before study entry. The *percentage of variability in measurement* was defined as the difference between the first and second readings, divided by the first reading. The limits of variation in all parameters of 2-D echos were 2.3% to 4.2%.

Exercise Test

Maximum symptom-limited exercise tests were performed on a treadmill using the slow US Air Force School of Aerospace Medicine protocol.¹² All patients were instructed to achieve the same level of perceived exertion during all tests.

Exercise duration was recorded at the end of each workload. We administered the exercise tests every day for 3 consecutive days from 2 to 4 days before the first treatment phase. The BP and heart rate (HR) before exercise (resting) and after exercise, as well as exercise duration, were recorded after blood sampling on the first day of the first and second treatment phases (baseline data). The reassessments at the end of both treatments were performed for comparison.

Neurohumoral Profile

Neurohumoral profile, including renin-angiotensin-aldosterone profiles (plasma renin activity [PRA], plasma aldosterone [ALD]) and sympathetic nervous system activation profiles (urinary epinephrine [E] and norepinephrine [NE]) profiles, were determined. All patients were asked to maintain their normal diet. We instructed all patients to fast after midnight before the mornings of blood sampling. We also asked them to sit quietly for 30 minutes before blood sampling. Fasting blood samples were drawn by an experienced laboratory technician for measuring PRA and ALD. Urine samples were collected over 24 hours on the same day, during which activities of daily living were performed for assessment of urinary E and NE levels. All baseline data were recorded on the first day of each treatment phase. The reassessments at the end of each treatment phase were done for comparison.

Tolerability Assessment

Tolerability was assessed using AEs recorded at patient interview.

Statistical Analysis

Continuous variables were summarized as mean (SD). All statistical analyses were performed using the Statistical Package for Social Sciences software version 10.0 (SPSS Inc., Chicago, Illinois). For multiple comparisons, the means of continuous variables were compared using 1-way analysis of variance, followed by the Scheffé test. Frequencies were analyzed by the Fisher exact test and continuity-adjusted chi-square test, where suitable. Comparisons of mean values were performed with paired and unpaired Student *t* tests. For all tests, a value of $P < 0.05$ was required for rejection of the null hypothesis.

RESULTS

Patient Population

A total of 33 patients were enrolled. As shown in the figure, of these 33 patients, 1 developed worsening HF during the run-in period and was admitted to the hospital. The remaining 32 patients (18 men, 14 women; mean [SD] age, 48.2 [6.3] years [range, 34–56 years]; mean [SD] SBP, 117.2 [9.8] mm Hg [range, 100–138 mm Hg]; mean [SD] DBP, 59.4 [5.7] mm Hg [range, 50–72 mm Hg]) entered the study. Vasodilators were being used in 25 patients (78.1%). All of

the vasodilators were ACE inhibitors. All 32 patients had moderate to severe HF, with New York Heart Association (NYHA) functional class III in 21 patients (65.6%) and class IV in 11 (34.4%) at the end of the run-in period before the study was started (**Table I**).

At the end of the run-in period, the mean dosages of diuretics and digitalis received by patients were furosemide 70 (15) mg/d and digoxin 0.65 (0.54) mg/d, respectively. This regimen was kept constant throughout the trial.

Sixteen patients (50.0%) were randomized to each treatment group. Table I indicates that the demographic data were similar in both groups before the start of the first treatment phase. **Table II** shows the data of the patients throughout the study. All parameters of the 32 patients entering the study, including SBP, DBP, HR, and clinical score at the end of the washout period before the second treatment phase returned to near-baseline values (mean [SD] difference in SBP, 0.50 [1.85]; in DBP, 0.07 [1.70]; in HR, -0.17 [1.18]; in clinical score, -0.13 [0.35]). In the first treatment phase, 1 patient (6.3%) withdrew from the group receiving felodipine, due to ankle edema; 1 patient (6.3%) withdrew from the group receiving fosinopril, due to intractable night cough. In the second treatment phase, 1 patient (6.3%) withdrew from the group receiving felodipine, due to worsening HF. We excluded 1 patient (6.3%) receiving felodipine in the second treatment phase due to poor compliance and 1 patient (6.3%) receiving felodipine who died of ovarian cancer. Therefore, 27 patients (13 women, 14 men; mean [SD] age, 47.7 [6.4] years [range, 34–56 years]) were included in the felodipine assessment and 30 patients (16 men, 14 women; mean

Table I. Demographic and clinical characteristics of study patients (N = 32).*

Characteristic	Felodipine (n = 16) [†]	Fosinopril (n = 16)
Demographic		
Age, y		
Mean (SD)	48.3 (6.1)	48.1 (6.5)
Range	37–56	34–56
Sex, no. (%)		
Men	10 (62.5)	8 (50.0)
Women	6 (37.5)	8 (50.0)
Clinical		
SBP, mean (SD), mm Hg	117.3 (10.2)	117.1 (9.7)
DBP, mean (SD), mm Hg	59.0 (5.1)	59.9 (6.4)
HR, mean (SD), bpm	80.8 (6.2)	81.6 (10.6)
NYHA class III, no. (%)	11 (68.8)	10 (62.5)
NYHA class IV, no. (%)	5 (31.3)	6 (37.5)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; NYHA = New York Heart Association.

*No significant between-group differences were found.

[†]Percentages may not add to 100 due to rounding error.

[SD] age, 48.3 [6.4] years [range, 34–56 years]) were included in the fosinopril assessment.

Efficacy

Symptomatic Assessment

The baseline mean (SD) clinical scores were 4.04 (0.19) with felodipine and 4.07 (0.25) with fosinopril. After 12 weeks of treatment, the mean (SD) clinical score with felodipine was 5.18 (0.48) and that with fosinopril was 5.27 (0.45). Significant symptomatic improvement compared with baseline was found with both treatments (both $P < 0.01$). The clinical scores did not differ significantly between the 2 treatments.

Echocardiography

Echocardiography data are shown in **Table III**. At baseline, the data of all parameters were similar in both groups. No significant change was found in any parameter after treatment with either drug compared with baseline, and no significant difference was found between treatments.

Exercise Test

No significant differences were found in resting SBP, DBP, and HR among 5 exercise tests before treatment: once a day for 3 consecutive days from 2 to 4 days before the first treatment phase and on the first day of first and second treatment phases. Also, no significant differences were found in exercise duration, attainment of SBP, DBP, and HR with exercise among 5 exercise tests before treatment: once a day for 3 consecutive days from 2 to 4 days before the first treatment phase and on the first day of first and second treatment phases.

Table IV shows the resting BPs and HRs at baseline and after treatment. Baseline resting BP and HR were similar between the 2 treatments. After treatment, resting SBP and DBP decreased significantly compared with baseline in both treatment groups (all $P < 0.01$). Moreover, after treatment, resting SBP and DBP were significantly lower with felodipine than with fosinopril ($P < 0.01$ and $P < 0.05$, respectively). With both treatments, resting HR did not change significantly after treatment compared with baseline. Resting HRs also were similar between treatments.

Table V shows the BPs and HRs achieved with exercise at baseline and after treatment. At baseline, SBP, DBP, and HR achieved with exercise were similar between treatments. After treatment, a significant decrease in SBP compared with baseline was found with felodipine ($P < 0.05$) but not with fosinopril. Also, after treatment, SBP with exercise was significantly lower with felodipine compared with fosinopril ($P < 0.05$). Finally, after treatment, significant decreases in HR with exercise were found with both felodipine and fosinopril versus baseline ($P < 0.01$ and $P < 0.05$, respectively). However, no significant difference was found after treatment in HR with exercise between groups. Furthermore, sig-

Table II. Patient data throughout the study (N = 32).

Patient No.	Age, y	Sex	SBP/DBP, mm Hg	HR, bpm	Drug Before Treatment*	Dosage, mg/d	NYHA Status	After First Treatment [†]			After Washout			After Second Treatment [‡]		
								SBP/DBP, mm Hg	HR, bpm	Clinical Score [‡]	SBP/DBP, mm Hg	HR, bpm	Clinical Score [‡]	SBP/DBP, mm Hg	HR, bpm	Clinical Score [‡]
1	53	M	124/60	80	Captopril	25	3	96/48	76	5	124/60	78	4	100/50	78	5
2	54	F	116/60	88	Captopril	25	3	92/50	84	5	114/60	88	4	104/46	86	5
3	56	M	110/52	86	Captopril	25	4	102/40	88	5	110/50	88	4	100/44	80	5
4	54	F	108/50	81	—	—	4	100/42	82	6	108/50	82	5	98/46	81	6
5	50	M	138/60	86	Enalapril	10	3	98/50	88	5	134/58	86	4	110/54	85	5
6	37	F	112/64	72	Fosinopril	10	3	104/52	71	6	112/62	75	4	112/54	84	5
7	45	M	120/60	70	Captopril	25	3	100/46	68	5	118/62	70	4	110/50	70	6
8	35	M	118/68	76	Enalapril	5	3	100/54	84	5	115/66	77	4	112/64	86	6
9	53	F	108/60	80	Fosinopril	10	3	106/52	84	5	108/60	80	4	114/60	78	5
10	50	M	124/60	94	Captopril	50	3	98/52	94	5	124/58	93	4	118/52	80	5
11 ^{III}	44	M	118/60	80	Fosinopril	10	3	—	—	—	(Ankle edema→stop)			—	—	—
12	50	F	110/56	82	Enalapril	5	4	98/42	78	6	108/58	82	5	96/52	81	5
13	49	M	102/50	80	—	—	4	88/40	78	5	102/48	79	4	90/42	86	5
14	43	M	106/66	78	—	—	3	86/50	78	5	102/66	78	4	90/50	77	5
15	47	F	130/58	74	Lisinopril	10	3	102/50	84	5	132/60	74	4	122/52	82	6
16	52	M	132/60	85	Enalapril	5	4	104/52	86	5	130/60	85	4	118/54	84	5
17 ^{III}	49	M	118/60	82	—	—	3	—	—	—	(Cough→stop)			—	—	—
18	34	M	122/72	57	Lisinopril	5	3	110/50	66	5	122/70	58	4	94/44	62	5
19 ^{II}	48	F	108/52	94	Perindopril	2	3	98/48	93	5	109/52	94	4	(Worsening HF→stop)		
20	44	M	110/60	84	Captopril	25	3	106/48	86	5	108/60	84	4	90/50	84	6
21 ^{II}	56	M	108/66	79	Quinapril	5	4	98/52	84	5	107/66	80	4	(Poor compliance→excluded)		

(continued)

Table II. (Continued)

Patient No.	Age, y	Sex	SBP/DBP, mm Hg	HR, bpm	Drug Before Treatment*	Dosage, mg/d	NYHA Status	After First Treatment†			After Washout			After Second Treatment‡		
								SBP/DBP, mm Hg	HR, bpm	Clinical Score‡	SBP/DBP, mm Hg	HR, bpm	Clinical Score§	SBP/DBP, mm Hg	HR, bpm	Clinical Score¶
22	48	M	132/58	95	Captopril	50	3	124/50	95	5	134/58	94	4	126/50	92	5
23	50	M	120/60	96	Fosinopril	5	3	108/54	86	5	118/62	96	4	102/50	94	5
24	55	M	116/54	90	Ramipril	1.25	3	108/50	85	6	116/56	90	5	(Died of cancer→excluded)		
25	52	F	130/50	72	—	—	4	120/46	80	6	128/48	74	4	88/40	73	5
26	55	M	106/60	70	Enalapril	5	4	94/60	74	5	108/62	72	4	90/50	80	6
27	44	F	130/66	76	Enalapril	10	3	118/50	74	5	130/64	76	4	114/46	74	5
28	49	F	100/50	73	—	—	4	90/46	76	5	100/50	74	4	84/44	82	6
29	54	F	114/60	80	Perindopril	2	3	104/60	84	5	114/64	80	5	98/50	80	5
30	51	F	116/70	84	Quinapril	5	4	104/54	86	5	118/72	82	4	92/62	80	4
31	45	F	114/60	92	—	—	3	102/48	80	6	112/60	90	4	90/44	89	5
32	35	F	130/60	82	Quinapril	5	4	110/54	85	6	134/58	82	4	98/46	78	5

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; NYHA = New York Heart Association; M = male; F = female; HF = heart failure.

*All patients were pretreated with digitalis/diuretics.

†First treatment was felodipine 2.5 mg/d in patients 1 to 16 and fosinopril 7.5 mg/d in patients 17 to 32.

‡Clinical score was set at 4 at the end of run-in before starting treatment.

§Second treatment was fosinopril 7.5 mg/d in patients 1 to 16 (patient no. 11 was excluded) and felodipine 2.5 mg/d in patients 17 to 32 (patient no. 17 was excluded).

||This patient did not complete felodipine treatment and was excluded from that analysis.

¶This patient did not complete fosinopril treatment and was excluded from that analysis.

Table III. Echocardiographic data before treatment (baseline) and after treatment (12 weeks).* (Values are expressed as mean [SD].)

Parameter	Felodipine 2.5 mg/d (n = 27)		Fosinopril 7.5 mg/d (n = 30)	
	Baseline	12 Weeks	Baseline	12 Weeks
LVDs, mm	58.8 (5.1)	58.3 (5.3)	58.3 (8.4)	59.2 (6.1)
LVDd, mm	66.3 (7.8)	64.9 (7.2)	66.2 (10.4)	65.3 (8.2)
EF, %	28.7 (11.2)	29.2 (8.4)	29.4 (13.1)	29.6 (12.3)
FS, %	15.4 (8.2)	15.3 (10.4)	14.6 (7.3)	16.3 (8.2)
LVMI, g/m ²	144.3 (25.2)	144.4 (20.2)	142.9 (25.3)	143.9 (22.2)

LVDs = left-ventricular end-systolic dimension; LVDd = left-ventricular end-diastolic dimension; EF = ejection fraction; FS = fractional shortening; LVMI = left-ventricular mass index.

*No significant between-group differences or within-group differences before versus after treatment were found.

nificant improvement in exercise duration was found with both treatments compared with baseline (felodipine: 366 [48] vs 248 [33] seconds; fosinopril: 370 [45] vs 244 [35] seconds; both $P < 0.01$ [data not shown]). No significant difference in exercise duration was found between treatments.

Neurohumoral Profile

Table VI shows the neurohumoral data before and after treatment. At baseline, the data for all parameters were similar between groups. PRA increased significantly versus baseline after treatment with fosinopril ($P < 0.01$). ALD did not change significantly with felodipine but was significantly decreased versus baseline with fosinopril ($P < 0.01$). Urinary E and NE were not significantly different between treatments or after treatment with either study drug compared with baseline.

Table IV. Resting blood pressure and heart rate (HR) before treatment (baseline) and after treatment (12 weeks). (Values are expressed as mean [SD].)

Clinical Characteristic	Felodipine 2.5 mg/d (n = 27)		Fosinopril 7.5 mg/d (n = 30)	
	Baseline	12 Weeks	Baseline	12 Weeks
SBP, mm Hg	117.9 (10.6)	97.8 (8.9)* [†]	116.6 (10.1)	106.3 (9.7)*
DBP, mm Hg	59.7 (6.0)	48.0 (5.0)* [‡]	59.2 (6.0)	51.3 (5.0)*
HR, bpm	80.5 (8.3)	81.1 (7.6)	81.3 (8.7)	81.7 (6.1)

SBP = systolic blood pressure; DBP = diastolic blood pressure.

* $P < 0.01$ versus baseline.

[†] $P < 0.01$ versus fosinopril.

[‡] $P < 0.05$ versus fosinopril.

Table V. Blood pressure and heart rate (HR) achieved with exercise before treatment (baseline) and after treatment (12 weeks). (Values are expressed as mean [SD].)

Clinical Characteristic	Felodipine 2.5 mg/d (n = 27)		Fosinopril 7.5 mg/d (n = 30)	
	Baseline	12 Weeks	Baseline	12 Weeks
SBP, mm Hg	148.3 (13.8)	135.8 (12.4)*†	150.4 (16.3)	146.1 (10.2)
DBP, mm Hg	88.4 (10.2)	86.9 (10.3)	90.3 (12.3)	87.8 (9.3)
HR, bpm	121.8 (17.3)	111.8 (11.7)‡	124.2 (19.3)	114.8 (10.3)*

SBP = systolic blood pressure; DBP = diastolic blood pressure.

* $P < 0.05$ versus baseline.

† $P < 0.05$ versus fosinopril.

‡ $P < 0.01$ versus baseline.

Tolerability

As shown in the figure and **Table VII**, 31 patients received felodipine and fosinopril, including 16 patients in both groups in the first treatment phase and 15 patients in both groups in the second treatment phase. No cardiac deaths or hospital admissions due to worsening HF occurred during the study. Eight patients experienced AEs with felodipine, and 7 patients experienced them with fosinopril. All of the AEs were considered treatment related. Worsening HF occurred in 2 patients (6.5%) with felodipine and in 2 patients (6.5%) with fosinopril. Among the patients with worsening HF, 1 of the 2 patients (50.0%) being treated with felodipine, but neither being treated with fosinopril, withdrew. Two patients withdrew due to AEs (1 due to ankle edema and 1 due to worsening HF) while receiving felodipine, and 1 patient withdrew due to an AE (intractable night cough) while receiving fosinopril. Twenty of 31 patients (64.5%) had cough while receiving fosinopril treatment ($P < 0.001$ vs felodipine).

Table VI. Neurohumoral profile before treatment (baseline) and after treatment (12 weeks). (Values are expressed as mean [SD].)

Parameter	Felodipine 2.5 mg/d (n = 27)		Fosinopril 7.5 mg/d (n = 30)	
	Baseline	12 Weeks	Baseline	12 Weeks
PRA, ng/mL·h	5.5 (4.1)	6.1 (3.9)*	5.4 (4.0)	9.8 (4.2)†
ALD, pg/mL	311.4 (139.0)	312.3 (124.9)‡	306.8 (142.2)	283.8 (129.2)†
E, µg/d	5.8 (3.1)	5.7 (2.7)	5.9 (3.0)	6.0 (3.5)
NE, µg/d	33.3 (21.0)	28.8 (16.0)	32.8 (21.5)	27.5 (14.9)

PRA = plasma renin activity; ALD = aldosterone; E = epinephrine; NE = norepinephrine.

* $P < 0.05$ versus fosinopril.

† $P < 0.01$ versus baseline.

‡ $P < 0.01$ versus fosinopril.

Table VII. Incidence of treatment-related adverse effects (AEs).^{*} (Values are expressed as no. [%] of patients.)

Parameter	Felodipine 2.5 mg/d (n = 31) [†]	Fosinopril 7.5 mg/d (n = 31) [†]
AE		
Ankle edema	7 (22.6) [‡]	0 (0.0)
Dizziness	2 (6.5)	2 (6.5)
Flushing	2 (6.5)	0 (0.0)
Worsening heart failure	2 (6.5)	2 (6.5)
Headache	1 (3.2)	0 (0.0)
Cough	0 (0.0)	20 (64.5) [§]
Patients with ≥ 1 AE	8 (25.8)	7 (22.6)
Withdrawals due to AE	2 (6.5)	1 (3.2) [¶]

^{*}Some patients had >1 AE.

[†]Tolerability assessment included 31 patients for each drug (16 patients in both groups in the first treatment phase and 15 patients in both groups in the second treatment phase).

[‡] $P < 0.01$ versus fosinopril.

[§] $P < 0.001$ versus felodipine.

^{||}One patient (3.2%) withdrew due to ankle edema and 1 patient (3.2%) withdrew due to worsening heart failure.

[¶]This patient withdrew due to intractable night cough.

Compliance rates for study medications were 93.5% (29/31) and 96.8% (30/31) with felodipine and fosinopril, respectively.

DISCUSSION

The objective of this study was a comparison of 12-week clinical effects, including symptomatic and hemodynamic profiles, in patients with nonischemic HF and normal BP who were treated with a standard drug for HF (the ACE inhibitor fosinopril) and a low-dose regimen of the second-generation CCB felodipine.

The present 12-week study using a low-dose drug regimen in patients with moderate to severe nonischemic HF and normal BP treated with an optimal regimen of digitalis and diuretics suggests that felodipine alone is similar to fosinopril alone as a vasodilator for improving symptoms and exercise performance, with no AEs on neurohumoral profiles. Also, low-dose felodipine in the present study was associated with tolerable AEs. These data are partly in accord with what was reported by de Vries et al,¹³ who conducted a parallel-group comparison and reported that vasodilation with felodipine and enalapril has comparable effects on exercise performance in patients with HF. Neither drug resulted in sympathetic activation. However, de Vries et al¹³ found that clinical improvement expressed as the score on quality-of-life questionnaires, particularly the general well-being index, showed only a little improvement. It is possible that de Vries et al¹³ had studied elderly patients (mean age,

65 years vs 48.2 years in the present study) with 80% ischemic heart disease (0% in the present study) and used a high dosage of felodipine (13 mg/d vs 2.5 mg/d throughout the present study). In V-HeFT III,⁹ felodipine 10 mg was tested against placebo in 451 male patients with mild to moderate HF and 55% showing ischemia, continuing ACE inhibitors, diuretics, and digoxin. No differences could be demonstrated after treatment comparing felodipine with placebo with regard to exercise duration and quality of life. Also, felodipine had no beneficial effect on patients with either ischemic or nonischemic causes of HF. In addition, in a small placebo-controlled crossover trial involving only 15 patients, Tan et al⁷ noted that felodipine 20 mg/d did not significantly improve symptom scores or exercise capacity in ischemic HF.

Whether HF is due to ischemia or not, the therapeutic dose of felodipine might be an important issue. An optimal clinical effect was observed as a result of a low dose of felodipine (2.5 mg/d) in the present study. However, no symptomatic improvement was shown with a high dose of felodipine used in the studies by de Vries et al¹³ (13 mg/d, 16 weeks), V-HeFT III⁹ (10 mg/d, 12 weeks), and Tan et al⁷ (20 mg/d, 3 weeks). High-dose felodipine might induce a hypotensive state in patients with nonischemic HF and normal BP, leading to deterioration in symptoms. However, it is not known whether Western patient populations with nonischemic HF and normal BP also benefit from a low-dose felodipine regimen. A study similar to the present one should be conducted in a Western patient population for clarification.

The present study had a 2-period crossover design. A 12-week treatment period was considered optimal for its purpose because too long a period on each treatment might lead to inadequate compliance with the protocol, a substantial number of patient withdrawals, and the disease condition not remaining sufficiently stable in some patients. Indeed, all 32 patients had moderate to severe HF before study entry, with 34.4% (11/32) having NYHA class IV status. It might have been unethical if the study had been extended beyond 12 weeks in patients having severe HF. The weakness of a crossover design is carryover effect and is discouraged in HF. In general, discontinuation of medication for 4 half-lives (the plasma half-life of felodipine in the extended-release formulation is 14 hours¹⁴) can eliminate most of the drug's effect. Thus, a 2-week washout period was introduced to diminish any carryover effect. Indeed, the clinical score and neurohumoral data returned to near-baseline values with both treatments at the end of the washout periods, indicating minimal carryover effect.

Exercise duration is a predictor of clinical improvement in patients with HF.¹⁵ No significant difference was found between the 2 treatment groups. The possibility of a training effect from exercise capacity should be considered. Our study indicated that BP, HR, and exercise duration measured in 3 tests at the end of the run-in period and 2 tests at the beginning of the treatment periods did not show significant differences, meaning that there might be no training effect from exercise testing. Also, a training effect is unlikely to be responsible

for the results because the physical tests were occasional and of short duration.⁵ HRs at rest and during exercise are strong indicators of sympathetic drive of the heart mediated by vasodilating therapy.¹⁶ A decrease in HR after therapy with the 2 treatments means a beneficial influence on neurohumoral response to vasodilation. Neurohumoral activity in the present study, as assessed using 24-hour urinary NE level, is consistent with findings of other investigators¹⁷ who measured plasma NE. However, plasma NE is probably less accurate because of the possibility of circadian rhythms. A decrease in 24-hour urinary NE levels after therapy is compatible with symptomatic improvement and testifies to the lack of reflex sympathetic activation. The 2-D echo parameters showed no significant improvement after either treatment. It is not surprising that 12-week treatment is not long enough to improve cardiac structure and function.

The present study had several limitations. First, a placebo-controlled study might be better in this situation. However, it is unethical to perform such a study with patients having such severe HF. Second, clinical score is a relatively insensitive method in HF assessment, although it is still widely used.⁷ A third and serious limitation is that patients might stop exercising, not because of dyspnea or fatigue but as a result of arrhythmia or lack of motivation, although exercise duration is widely used for the assessment of drugs in HF. Submaximal exercise testing protocols assess submaximal workload and compare exercise levels below peak exercise levels, which are more objective and more in accord with activities of daily living.¹⁸ The fourth and most important study limitation is that short-term symptom relief and hemodynamic improvement may not correlate with long-term clinical outcome. The sample size of the study is not large enough to assess equivalence of felodipine and fosinopril. A larger number of patients with a longer treatment course seems necessary for a rational clinical assessment, but again, ethical problems should be considered in patients having severe HF. Furthermore, the neurohumoral systems that are activated in patients with HF include not only the sympathetic nervous system and the renin-angiotensin system but also vasopressin and atrial natriuretic peptide. Thus, the latter 2 measurements are necessary to truly determine neurohumoral effect.

CONCLUSIONS

Symptoms, exercise capacity, and neurohormone levels were used as indexes for comparison between fosinopril and felodipine. The present findings suggest that, in Chinese patients with moderate to severe HF who have normal BP and insignificant coronary artery disease and were being treated with diuretics and digitalis, a 12-week, low-dose course of felodipine (2.5 mg/d) as a vasodilator was associated with as satisfactory an outcome as standard treatment with fosinopril (7.5 mg/d).

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