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Comparative Effects of Fosinopril and Nifedipine on Regression of Left Ventricular Hypertrophy in Hypertensive Patients: A Double-Blind Study

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Summary. **The effects of fosinopril and nifedipine on left ventricular (LV) mass were evaluated in 35 hypertensive patients with LV mass index greater than 110 g/m^2 in female and 130 g/m^2 in male patients. The goal of therapy was also to obtain a seated diastolic blood pressure (SDBP) of less than 90 mmHg. The patients were studied by echocardiography after 2 weeks of placebo treatment and 4, 12, and 24 weeks of monotherapy with active drugs. Both fosinopril and nifedipine reduced SDBP to a normal level after 6 months of treatment ($p < .001$). Regression of LV hypertrophy was achieved by either agent ($p < .001$), with fosinopril being more effective than nifedipine ($p < .002$). In conclusion, both fosinopril and nifedipine effectively reduce SDBP and achieve important regression of LV hypertrophy.**
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Key Words. **fosinopril, essential hypertension, nifedipine, left ventricular hypertrophy, regression**

According to numerous clinical trials, it is known that various antihypertensive drugs, and particularly angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists, have proven to have a noticeable degree of efficacy on regression of left ventricular (LV) hypertrophy [1–7]. LV hypertrophy is the response of the heart to chronic pressure and/or volume overload. It is characterized by increased LV internal dimension and/or wall thickness.

The traditional approach to the diagnosis of LV hypertrophy was through its electrocardiographic appearance. In the Framingham study the prevalence of LV hypertrophy using these criteria is low [8,9]. In contrast to electrocardiography, echocardiography permits precise visualization of cardiac structures and calculation of LV mass [10].

This study evaluated the regression of LV hypertrophy in hypertensive patients treated with fosinopril or nifedipine, in parallel with lowering seated diastolic blood pressure (SDBP). Fosinopril is the first compound in a new class of ACE inhibitors that contains a phosphate group capable of binding to the active site of ACE inhibitors [11]. Nifedipine is an established dihydropyridine calcium antagonist with a definite place in the treatment of arterial hypertension.

Patients and Methods

Patients

Thirty-two consecutive hypertensive outpatients were enrolled, and 31 completed the study (23 women and 8 men). The mean age was 60.4 ± 3.9 years. The diagnosis of essential hypertension was established by history and physical examination, with the absence of clinical findings suggestive of a secondary form of hypertension. Inclusion criteria for admission were SDBP between 95 and 110 mmHg in two separate determinations during a 2-week run-in period and LV mass index greater than 110 g/m^2 in female and 130 g/m^2 in male patients in two M-mode echocardiographic determinations taken 2 weeks apart during the run-in period. Exclusion criteria were cardiovascular diseases (myocardial infarction within the previous 6 months, congestive heart failure, heart block), renal diseases, and renal failure (serum creatinine greater than 1.5 mg/dl), insulin-dependent diabetes mellitus, obesity over 30% ideal bodyweight, and psychiatric problems. Each patient gave informed consent, and the study was also approved by the National Ethical Committee.

After a 14-day run-in period with placebo, patients with persistent diastolic pressure of 95–110 mmHg were qualified for active treatment in a double-blind 24-week controlled trial with fosinopril 20 mg once daily (16 patients), or nifedipine 20 mg twice daily (15 patients). The drugs were supplied by the Bristol-Myers Squibb Company. At the end of the first 8 or 12 weeks, those patients whose SDBP remained greater than 95 mmHg, received hydrochlorothiazide 25 mg once daily, added to the standard regimen of the study drug.

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Methods

Blood pressure was measured by mercury sphygmomanometer after 10 minutes at rest in the seated position, taking three measurements in 5 minutes. The average of the three readings was recorded as the Korotkof V for diastolic blood pressure. Blood pressure was measured at the entry visit, at the end of the placebo period, after 2 weeks of therapy, and at the end of the first, second, third, and sixth months of therapy.

Echocardiographic study was performed with the use of a Diasonics' series 250 Ultrasonic imaging system, with the patient in the left decubitus position, using a 3 mHz transducer. All two-dimensional guided M-mode tracings were recorded by the same cardiologist and were read blindly in random order, without knowledge of the blood pressure value at the time that the echocardiogram was recorded. LV measurements included end-diastolic and end-systolic diameters (EDD and ESD), intraventricular septal thickness (IVS), and posterior wall thickness (PW) at end diastole and end systole. From these measurements the LV mass index was derived according to the Penn convention [12,13].

Statistical analysis

Data are expressed as means ± standard deviation. Statistical analyses were performed using the Student t test for paired or unpaired data. A probability $p < .05$ was considered significant.

Results

Patient characteristics regarding age, gender, baseline diastolic blood pressure, and baseline echocardiographic findings are shown in Table 1. Both fosinopril (Table 2) and nifedipine (Table 3) reduced blood pressure to a normal level after 6 months of therapy ($p < .001$). SDBP was reduced to a value of less than 90 mmHg in 11 of 16 patients treated with fosinopril and in 8 of 15 patients treated with nifedipine. The difference between the two agents was not statistically significant.

Hydrochlorothiazide was added to the therapy for five patients in the fosinopril group and seven patients in the nifedipine group. Blood pressure reduced to more than 95 mmHg in one patient of each group. There were no differences in heart rate (HR) changes between the two groups.

LV mass index was decreased significantly with both medications ($p < .001$). The magnitude of reduction after 6 months was greater with fosinopril (14.8%) than with nifedipine (9.4%), and this difference was significant ($p < .002$) (Tables 2 and 3).

Discussion

It has long been known that hypertension induces LV hypertrophy and that hypertensive patients with LV hypertrophy have a particularly adverse prognosis [14–15]. Electrocardiographic methods are of limited use, identifying high-risk patients in about 5% of average patients with hypertension. This situation has changed since echocardiography allows accurate assessment of the magnitude of LV hypertrophy and its changes over time [10]. Calculating LV mass index appears desirable when the goal is to detect LV hypertrophy due to a pathologic condition, such as hypertension [16–17]. Reversal of LV hypertrophy has been reported not to occur with all antihypertensive agents. ACE inhibitors and calcium antagonists have been proven to decrease LV mass in parallel with arterial pressure.

Our study demonstrated that the antihypertensive efficacy of fosinopril and nifedipine is similar. Both agents were effective in reducing diastolic blood pressure ($p < .001$). With regard to regression of LV hypertrophy, fosinopril was more effective than nifedi-

Table 1. *Patient characteristics*

	Fosinopril group	Nifedipine group	p
Age (years)	59.1 ± 3.3	61.2 ± 4.2	NS
Sex (male/female)	4/12	4/11	NS
Baseline SDBP (mmHg)	102.8 ± 7	103.6 ± 6	NS
Baseline LVMi (g/m^2)	145.5 ± 17	146.4 ± 14	NS

SDBP = seated diastolic blood pressure; LVMi = left ventricular mass index; NS = not significant.

Table 2. *Seated diastolic blood pressure (SDBP), heart rate (HR), intraventricular septum thickness (IVS), posterior wall thickness (PW), and left ventricular mass index (LVMi) at baseline and after 6 months of treatment with fosinopril*

	Baseline	6 months	p
SDBP (mmHg)	102.8 ± 7	85.1 ± 6	<.001
HR (min^{-1})	73 ± 8	71 ± 9	NS
IVS (mm)	12.7 ± 0.9	11.5 ± 0.8	<.001
PW (mm)	11.4 ± 0.8	10.6 ± 0.7	<.001
LVMi (g/m^2)	145.5 ± 17	123.9 ± 14	<.001

Table 3. *Seated diastolic blood pressure (SDBP), heart rate (HR), intraventricular septum thickness (IVS), posterior wall thickness (PW), and left ventricular mass index (LVMi) at baseline and after 6 months of treatment with nifedipine*

	Baseline	6 months	p
SDBP (mmHg)	103.6 ± 6	89.3 ± 5	<.001
HR (min^{-1})	72 ± 9	75 ± 7	NS
IVS (mm)	12.8 ± 1.0	11.8 ± 0.9	<.001
PW (mm)	11.6 ± 0.9	10.9 ± 0.8	<.001
LVMi (g/m^2)	146.4 ± 14	132.7 ± 13	<.001

pine ($p < .002$), but both agents achieved a significant reduction of LV mass ($p < .001$).

The five patients treated with fosinopril and the seven patients treated with nifedipine who failed to achieve blood pressure normalization had no LV mass reduction. This is in addition to the fact that ACE inhibitors and calcium antagonists induce a regression of LV hypertrophy in the presence of prolonged blood pressure reduction [18–19], although studies with opposite indications exist. All these patients received hydrochlorothiazide 25 mg once daily added to active treatment, but only one patient in each group achieved blood pressure normalization. This probably occurred because of the low dose of the diuretic used.

There are many studies comparing ACE inhibitors with calcium antagonists, a number of which testify to the approximate equivalence of the antihypertensive effects of both types of agents [20–24]. The comparison of various pharmacologic agents with regard to the magnitude of LV mass regression is related to their distinct effects on reversing hypertrophy. Reduction of cardiac mass takes place through a variety of mechanisms, including the availability of intracellular calcium ions or inhibition of the cardiac myocytic renin angiotensin system [25,26]. Thus pharmacologic interference with these factors by either medication could participate independently in the reversal of LV hypertrophy.

It should be noted that when one treats any patient with hypertension for a long enough period with ACE inhibitors or calcium antagonists, cardiac mass will decrease in association with the control of hypertension. Finally, one would need a higher number of patients and a longer observation period before making any definitive conclusions, as fosinopril is a new ACE inhibitor and requires more testing.

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