Effect of Fosinopril on Cardiac and Metabolic Parameters in Patients With NIDDM

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OBJECTIVE — To determine whether the angiotensin-converting enzyme (ACE) inhibitor fosinopril can favorably alter cardiac function in non-insulin-dependent diabetes mellitus (NIDDM) patients who have either normal blood pressure (BP) or mild, untreated hypertension.

RESEARCH DESIGN AND METHODS — Fifty-five NIDDM subjects with normal BP or mild, untreated hypertension were randomized to treatment with the ACE-inhibitor fosinopril or placebo for 6 months in a randomized, double-blind trial to determine the effect of fosinopril on echocardiographic measurements.

RESULTS — Left ventricular mass index (LVMI) fell by 6.5 ± 4.7% (mean ± SD) with fosinopril and increased by 8.6 ± 3.5% during placebo treatment ($P < 0.02$), and isovolumic relaxation time improved significantly in those with elevated baseline levels ($P = 0.02$). Systolic BP fell significantly, but this did not correlate with the change in LVMI, suggesting a possible direct action of fosinopril on the heart.

CONCLUSIONS — Fosinopril appears to have significant cardiac benefits in patients with NIDDM who have normal or mildly elevated BP. These benefits are achieved without adversely affecting renal status and without impairing metabolic control of diabetes.

Non-insulin-dependent diabetes mellitus (NIDDM) is frequently associated with other cardiovascular risk factors, such as hyperlipidemia and hypertension (1), and patients with this disorder frequently have abnormal cardiac function (2). Angiotensin-converting enzyme (ACE) inhibitors have been found to improve cardiac function in hypertensive subjects with heart disease (3). In this study, an ACE inhibitor has been used to determine whether cardiac function can be favorably altered in NIDDM subjects with either normal blood pressure (BP) or untreated mild hypertension.

RESEARCH DESIGN AND METHODS

— Patients with NIDDM and no history of known hypertension, cardiac disease, or treatment with cardiovascular medications were chosen for study. Those with gross obesity (body mass index [BMI] >40 kg/m^2) were excluded to avoid technical problems with echocardiography. Control subjects for echocardiography were nondiabetic, normotensive individuals matched for sex, age, and BMI with the study group. Ethical approval for the study was obtained from the Auckland Area Health Board Ethics Committee, and informed consent was obtained from all participants.

A randomized, double-blind, placebo-controlled, parallel design study was carried out with a 4-week placebo pretreatment phase, followed by baseline echocardiographic and metabolic measurements. Subjects were then randomized to either fosinopril or placebo treatment: 10 mg daily for 4 weeks, then increased to 20 mg daily. After 26 weeks of treatment, the tests were repeated. Treatment groups were stratified according to BMI and sex. Adverse effects were recorded every 4 weeks throughout the study. Two-dimensional, guided M-mode and Doppler echocardiography was carried out by one observer, with measurements over three cardiac cycles. Left ventricular mass index (LVMI) was obtained from parasternal M-mode measurements (4) and ventricular dimensions (5), and diastolic function (6) and isovolumic relaxation time (IVRT) (6) were measured by standard techniques. Measurements included E velocity, A velocity, acceleration time, deceleration time, early filling

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NIDDM, non-insulin-dependent diabetes mellitus, ACE, angiotensin-converting enzyme; BP, blood pressure; BMI, body mass index; LVMI, left ventricular mass index; IVRT, isovolumic relaxation time; sBP, systolic blood pressure; dBP, diastolic blood pressure.

Table 1—*Baseline characteristics of treated patients*

	Placebo	Fosinopril	Total group
n	24	31	55
Sex (M/F)	15/9	16/15	31/24
Age (years)	56.6 ± 2.0	54.6 ± 1.6	55.4 ± 1.2
BMI (kg/m^2)	28.0 ± 0.8	28.6 ± 0.6	28.3 ± 0.5
Waist-to-hip ratio	0.92 ± 0.01	0.90 ± 0.01	0.91 ± 0.01
Duration of diabetes (years)	5.3 ± 1.11	6.0 ± 1.3	5.7 ± 0.9
Sitting sBP (mmHg)	140.9 ± 2.8	138.3 ± 1.8	139.5 ± 1.6
Sitting dBP (mmHg)	86.6 ± 1.4	85.3 ± 1.3	85.9 ± 1.0

Data are means ± SE.

time (E), late filling time (A), and IVRT. Sitting BP was measured at 0900, ~2 h after morning medication, using a Hawkesley random zero sphygmomanometer. Blood lipids were measured in a World Health Organization registered reference laboratory, and diabetic glycemic control was assessed by fasting blood glucose, serum fructosamine, and capillary blood glucose measurements. Insulin resistance was measured at the beginning and end of the study by continuous infusion of glucose with model assessment (7).

Statistical analysis

Data were analyzed by a multivariate approach to repeated measures using SAS software (8). Results are presented as the F-approximation to the Hotelling-Lawley trace. Data are also expressed as the change from baseline to remove between-subject variation. Correlations between variables were sought using Spearman's procedure and all tests were two-tailed.

RESULTS— Of the 55 patients who began the study, 50 completed treatment. Patient characteristics at baseline are shown in Table 1. There were no significant differences between treatment groups. Fifty-five percent of the total group had mild hypertension (9) (baseline BP >140/90): 16 in the placebo group and 14 in the fosinopril group.

The results of baseline echocardiography are shown in Table 2. NIDDM subjects had significantly abnormal IVRT, circumferential shortening, and in women, LVMI. Of the total group, 23% had an LVMI >2 SDs beyond the control mean, 8% had an abnormal IVRT, and 33% had an abnormally low E:A ratio. Within the total group of NIDDM subjects, the basal E:A ratio was negatively correlated with systolic blood pressure (sBP) ($r = 0.58$, $P < 0.05$) but not with diastolic blood pressure (dBP). The baseline LVMI was positively correlated with sBP ($r = 0.45$, $P < 0.01$) and also showed a weak correlation with the extent of basal microalbuminuria ($P = 0.06$).

The effects of treatment are shown in Table 3. In the men, the mean LVMI changed significantly both between groups and within the fosinopril-treated patients; measurements improved in those on fosinopril and deteriorated in those on placebo. This was principally due to a reduction in ventricular wall thickness, since left ventricular end-diastolic dimension did not change significantly (data not shown). A fall in LVMI with fosinopril was also apparent in the women, although this did not reach statistical significance. Combined data from both sexes showed a significant overall reduction in LVMI of 6.5 ± 4.7% in those on fosinopril compared with an increase of 8.6 ± 3.5% in those on placebo. The peak E velocity deteriorated significantly during placebo treatment, and there was a trend for the E:A ratio to worsen also, whereas mean levels were maintained on fosinopril. The difference between groups was not, however, statistically significant, even when the analysis was restricted to those with abnormal E:A ratio at baseline. The reduction in E:A ratio in the whole group during the study was positively correlated with the known duration of diabetes ($r = 0.38$, $P < 0.02$). There was a trend for IVRT to improve in the fosinopril group, and this was significant in

Table 2—*Baseline echocardiographic data*

	Normal subjects (*n* = 18)	Patients (*n* as shown)
LVMI (g/m^2)		
Men	88.8 ± 12.5	95.8 ± 26.1 (26)
Women	72.1 ± 21.7	91.0 ± 27.9* (17)
r/th ratio	2.97 ± 0.38	2.4 ± 0.42* (43)
Fractional shortening (%)	36.8 ± 6.2	35.9 ± 7.0 (43)
VCF (circ/s)	1.3 ± 0.4	1.1 ± 0.2* (35)
Deceleration time (ms)	167.0 ± 56.5	178.3 ± 52.7 (42)
IVRT (ms)	70.9 ± 16.7	83.7 ± 16.9* (36)
Peak E velocity (m/s)	55.4 ± 8.1	56.5 ± 16.5 (42)
Peak A velocity (m/s)	49.3 ± 4.2	60.3 ± 11.1* (42)
E: A ratio		
<50 years of age	1.3 ± 0.11	1.21 ± 0.38 (9)
>50 years of age	1.1 ± 0.19	0.88 ± 0.21 (33)

Data are means ± SD; *n* varies according to the number of echocardiograms from which valid measurements could be obtained. *$P < 0.05$. r/th, radius/wall thickness; VCF, velocity of circumferential fiber shortening.

Table 3—*Change in echocardiographic variables with treatment*

	Placebo group (n = 19)		Fosinopril group (n = 24)	
	Basal	6 months	Basal	6 months
LVMI (g/m^2)				
Men	97.6 ± 22.6 (12)	102.0 ± 22.8 (12)	94.3 ± 29.6 (14)	83.2 ± 27.7* (13)
Women	94.4 ± 37.7 (7)	101.0 ± 32.7 (5)	88.6 ± 29.6 (10)	82.5 ± 26.1 (9)
r/th ratio	2.44 ± 0.43	2.49 ± 0.47	2.48 ± 0.53	2.58 ± 0.60
Fractional shortening (%)	34.66 ± 6.2	32.7 ± 8.3	37.0 ± 7.5	36.2 ± 8.7
VCF (circ/s)	1.0 ± 0.14	1.1 ± 0.23	1.17 ± 0.24	1.17 ± 0.36
Deceleration time (ms)	194.7 ± 59.1	204.1 ± 54.1	187.3 ± 56.2	186.1 ± 53.9
IVRT (ms)	82.9 ± 16.3	80.9 ± 17.7	84.3 ± 17.8	75.9 ± 11.8
Peak E velocity (m/s)	55.7 ± 18.2	47.3 ± 12.6†	57.1 ± 15.4	53.9 ± 9.7
Peak E velocity (m/s)	61.5 ± 11.3	59.5 ± 12.3	59.3 ± 11.1	59.2 ± 10.4
E: A ratio				
<50 years of age	1.22 ± 0.46	1.13 ± 0.34	1.20 ± 0.36	1.09 ± 0.24
>50 years of age	0.83 ± 0.18	0.73 ± 0.16	0.92 ± 0.21	0.88 ± 0.23

Data are mean ± SD; (n). *P < 0.05 different from placebo and from baseline. †P < 0.05 significantly different from baseline.

those patients who had elevated baseline IVRT levels (P = 0.02).

sBP fell significantly (mean ± SD: fosinopril 8.7 ± 12 mmHg, placebo 3.3 ± 14 mmHg, P < 0.01) during the study, but there was no significant change in dBP. The reduction in LVMI showed no significant correlation with the fall in sBP. There was no significant group change in mean body weight, serum lipids, glucose control, hematology, liver function tests, or renal function during the study. There was a nonsignificant trend for microalbuminuria to lessen during fosinopril treatment (mean ± SD: 14.6 ± 11.8 μg/min at baseline, 13.2 ± 14.1 μg/min on placebo, and 11.4 ± 13 μg/min on fosinopril). Insulin sensitivity did not change significantly; neither did fasting serum insulin, C-peptide, insulin:glucose ratios, glucose, or fructosamine.

Five patients withdrew from the trial: one in the fosinopril group (because of cough and indigestion) and four in the placebo group (one lost to follow-up, one because of myocardial infarction, one because of atrial fibrillation requiring cardiac medication, and one with Meniere's disease). There was no significant difference in reported adverse effects between the fosinopril and placebo groups.

CONCLUSIONS— In this study, patients with NIDDM showed several cardiac abnormalities, despite a normal mean BP in the total group, a relatively short duration of diagnosed diabetes (mean = 5.7 years), normal albumin excretion and renal function, and reasonable glucose control as judged by a mean serum fructosamine value only slightly above normal. The observed echocardiographic abnormalities were seen equally in those with normal or mildly elevated BP. Fosinopril treatment was associated with a significant reduction in LVMI and a trend to improvement in cardiac diastolic function; this did not relate to BP reduction, which suggests a direct action of fosinopril on the myocardium (10). Others have found greater regression of left ventricular hypertrophy with ACE inhibitors than other antihypertensive drugs for similar BP reduction (3). The present results are similar to those obtained by Zusman et al. (11) and Oren et al. (12).

Fosinopril had no significant effect on lipid levels, glycemic control, microalbuminuria, or renal function and did not impair insulin sensitivity. Since NIDDM subjects may have some degree of renal impairment, the unique hepatobiliary excretion of fosinopril may protect against drug accumulation and toxic effects of ACE inhibitors in these patients. An improvement in urinary albumin excretion with fosinopril treatment has been found by others (13), but the effect in patients with microalbuminuria has not been studied. Keilani et al. (13) also found reduced serum lipids with fosinopril, but their patients had significant proteinuria and thus differed from those in the present study.

Overall, fosinopril appears to have significant cardiac benefits in patients with NIDDM who have normal or mildly elevated BP. These benefits are achieved without adversely affecting renal status and without impairing metabolic control of diabetes. It appears a safe and well-tolerated agent that may have particular benefits in this patient subgroup.

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