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Effectiveness and Safety of Diltiazem or Lisinopril in Treatment of Hypertension After Heart Transplantation

Results of a Prospective, Randomized Multicenter Trial

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Objectives. **The purpose of this study was to determine the effectiveness and safety of diltiazem or lisinopril for treatment of hypertension after heart transplantation.**

Background. **Systemic hypertension is common after heart transplantation, and to date there are no randomized, prospective multicenter treatment trials.**

Methods. **Members of the Cardiac Transplant Research Database Group developed and implemented a prospective, randomized multicenter trial of the effectiveness and safety of diltiazem or lisinopril in the treatment of hypertension in cyclosporine-treated patients after heart transplantation.**

Results. **One hundred sixteen patients with hypertension (blood pressure ≥140/90 mm Hg) after heart transplantation were randomized for ≥3 months of treatment. Of 55 diltiazem-treated patients, 21 (38%) were responders (diastolic blood pressure <90 mm Hg), 23 (42%) were nonresponders (diastolic blood pressure ≥90 mm Hg), and 11 (20%) were withdrawn from the study. Of 61 lisinopril-treated patients, 28 (46%) were responders, 22 (36%) were nonresponders, and 11 (18%) were withdrawn. There was no difference in baseline characteristics or percent responders between the two groups. Systolic pressure decreased from 157 ± 2.3 to 130 ± 2.0 mm Hg (mean ± 1 SEM) in the diltiazem-treated responders and from 153 ± 2.1 to 127 ± 2.7 mm Hg in the lisinopril-treated responders ($p < 0.0001$). Diastolic pressure decreased from 100 ± 0.9 to 85 ± 1.6 mm Hg in the diltiazem-treated responders and from 100 ± 1.0 to 84 ± 2.0 mm Hg in the lisinopril-treated responders ($p < 0.0001$). There were a total of 35 reported adverse events, 22 of which led to withdrawal of the patient from the study. All drug-related side effects were considered minor and resolved with discontinuation of the drug.**

Conclusions. **These results indicate that both diltiazem and lisinopril are safe for treatment of hypertension after heart transplantation, although titrated monotherapy with either drug controlled the condition in <50% of patients.**

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Systemic hypertension, one of the most common complications occurring in patients after heart transplantation, has a reported incidence rate of >90% (1–4). It is often difficult to treat, and many patients require more than one antihypertensive agent for control.

To our knowledge, this study is the first prospective, randomized multicenter trial of the treatment of hypertension after heart transplantation in patients receiving cyclosporine therapy. The purpose of this study was to determine the effectiveness and safety of diltiazem or lisinopril for treatment of hypertension after transplantation.

Methods

Study patients. Eleven centers of the Cardiac Transplant Research Database Group participated in this study (see Appendix). Each center had individual approval from its respective Institutional Review Board. Patients were eligible for the study if they were ≥18 years of age, had undergone heart transplantation in the preceding 1 to 12 months, were

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being treated with cyclosporine and had a supine blood pressure ≥140/90 mm Hg on ≥3 separate days despite a restricted sodium diet. All patients gave written informed consent. Patients were excluded if they had known sensitivity to lisinopril, diltiazem or any angiotensin-converting enzyme–inhibiting drug; accelerated or malignant hypertension; serum creatinine >2.5 mg/dl; or second- or third-degree atrioventricular (AV) block unless a normally functioning pacemaker was present.

Protocol. Patients were randomized to receive either diltiazem or lisinopril. Treatment with sustained-release diltiazem was started at 90 mg, twice daily; the dose could be increased weekly up to a maximal daily dose of 360 mg. Given diltiazem's effect of increasing cyclosporine levels, cyclosporine doses were adjusted accordingly. Treatment with lisinopril was started at a dose of 10 mg daily; the dose could be increased weekly to a maximal dose of 40 mg daily. All patients were seen every 1 to 2 weeks during the titration phase. Once blood pressure control or maximal dose was attained, patients were followed up for 2 months and seen at least monthly. Weight and blood pressure measurements (average of two successive blood pressure readings), a brief examination and review of side effects and concomitant medications were performed at each visit, and any intercurrent rejection episodes were recorded. Laboratory studies included a complete blood count, routine blood chemistry determinations, and cyclosporine level. Patients receiving diltiazem had an electrocardiogram (ECG) performed if the dose had been increased. Diuretic drugs were used on an as-needed basis only for treatment of edema as deemed appropriate by the investigator.

Patients were withdrawn from the study for serious events such as rejection with hemodynamic compromise, severe infection, renal failure, hyperkalemia, angioedema or heart block.

Choice of drugs. The investigators chose to examine the effects of two different classes of vasodilators—calcium-channel antagonists and angiotensin-converting enzyme inhibitors—because of the collective clinical experience with these two classes of drug. Diltiazem was chosen as the calcium channel antagonist because of its favorable effect on cyclosporine level. Lisinopril was chosen as the angiotensin-converting enzyme inhibiting drug because it is effective with once-daily dosing.

Statistical analysis. All data were entered and analyzed at the CTRD Data Coordination and Analysis Center at the University of Alabama at Birmingham. The success of diltiazem and lisinopril were compared by a chi-square test for comparing proportions of success for the two drugs. Data are reported as mean value ± 1 SEM. Patients were considered responders if they maintained a supine diastolic blood pressure <90 mm Hg and nonresponders if they had a supine diastolic blood pressure ≥90 mm Hg with maximal dose of the study drug. Changes in cyclosporine levels were compared within and between the groups by using two-way repeated measures analysis of variance.

Table 1. Baseline Data

	Total Group (n = 116)	Diltiazem (n = 55)	Lisinopril (n = 61)
Age (yr)	52 ± 1.5	55 ± 1.3	53 ± 1.2
Male (%)	80	80	80
Months after transplantation	3.4 ± 0.24	3.3 ± 0.36	3.4 ± 0.33
Creatinine (mg/dl)	1.46 ± 0.03	1.46 ± 0.05	1.46 ± 0.04
Initial systolic BP (mm Hg)	155 ± 1.0	155 ± 1.4	155 ± 1.5
Initial diastolic BP (mm Hg)	102 ± 0.6	102 ± 1.0	101 ± 0.8
Daily prednisone (mg/kg body weight)	0.12 ± 0.01	0.12 ± 0.02	0.11 ± 0.01
Daily cyclosporine (mg/kg body weight)	2.8 ± 0.11	2.9 ± 0.19	2.7 ± 0.12

There are no significant differences between groups. Unless otherwise indicated, data are presented as mean value ± 1 SEM. BP = blood pressure.

Results

Baseline data. Of 116 randomized patients, 94 (81%) completed the protocol and 22 (19%) were withdrawn from the study because of adverse events. Table 1 shows baseline data for the initial 116 patients and the two randomized groups. There was no significant difference among groups in age, gender, time after transplantation, serum creatinine level, initial blood pressure or daily doses of cyclosporine and prednisone at study entry.

Drug efficacy. Of the 55 patients receiving diltiazem, 21 (38%) were responders (95% confidence limits [CL] 26%, 52%), 23 (42%) were nonresponders (95% CL 29%, 56%) and 11 (20%; 95% CL 11%, 33%) were withdrawn from the study because of adverse events. Of the 61 patients receiving lisinopril, 28 (46%) were responders (95% CL 33%, 59%), 22 (36%) were nonresponders (95% CL 24%, 49%) and 11 (18%; 95% CL 10%, 30%) were withdrawn from the study because of adverse events. There were no differences between the patient groups receiving diltiazem or lisinopril in terms of percent responders, nonresponders and patients withdrawn from the study. Table 2 compares results among responders, nonresponders and patients withdrawn from the study in each drug treatment group.

There were no differences among the responders, nonresponders and patients withdrawn from the study with respect to age, gender, time after transplantation, initial cyclosporine and prednisone doses, final cyclosporine dose, initial creatinine level or initial blood pressure measurements. Responders in both treatment groups had a significant difference in systolic and diastolic blood pressure. The magnitude of change in the systolic and diastolic blood pressure measurements (Fig. 1) did not differ between the two treatment groups. Systolic pressure decreased from 157 ± 2.3 to 130 ± 2.0 mm Hg in the diltiazem-treated responders ($p < 0.0001$) and from 153 ± 2.1 to 127 ± 2.7 mm Hg in the lisinopril-treated responders ($p < 0.0001$) with an average daily dose of 18 ± 2.2 mg. Diastolic pressure decreased from 100 ± 0.9 to 85 ± 1.6 mm Hg in the diltiazem-treated responders ($p < 0.0001$) and from 100 ± 1.0 to 84 ± 2.0 mm Hg in the

Table 2. Results in Responders, Nonresponders and Patients Withdrawn From the Study

	Diltiazem			Lisinopril		
	R (n = 21)	NR (n = 23)	W (n = 11)	R (n = 28)	NR (n = 22)	W (n = 11)
Age (yr)	52 ± 1.5	50 ± 2.1	52 ± 2.9	51 ± 2.1	55 ± 1.4	52 ± 1.9
Male (%)	81	83	73	79	91	64
Months after transplantation	3.6 ± 0.6	3.4 ± 0.5	2.7 ± 0.9	3.7 ± 0.6	2.5 ± 0.2	4.4 ± 0.9
Cyclosporine (mg/kg body weight)						
Initial	3.1 ± 0.35	2.8 ± 0.27	3.0 ± 0.38	2.7 ± 0.17	2.6 ± 0.22	2.8 ± 0.25
Final	2.6 ± 0.62	2.2 ± 0.34	2.8 ± 0.68	2.1 ± 0.32	3.2 ± 0.53	3.0 ± 0.09
Prednisone (mg/kg body weight)						
Initial	0.11 ± 0.01	0.15 ± 0.05	0.11 ± 0.01	0.11 ± 0.01	0.1 ± 0.01	0.11 ± 0.03
Creatinine (mg/dl)						
Initial	1.36 ± 0.07	1.62 ± 0.08	1.35 ± 0.11	1.43 ± 0.06	1.40 ± 0.06	1.65 ± 0.12
Final	1.54 ± 0.09*	1.59 ± 0.07	1.68 ± 0.24	1.55 ± 0.08	1.68 ± 0.05†	1.90 ± 0.19
Systolic BP (mm/Hg)						
Initial	157 ± 2.3	153 ± 2.0	156 ± 3.0	153 ± 2.1	160 ± 2.7	153 ± 3.6
Final	130 ± 2.0‡	150 ± 4.1	134 ± 8.0	127 ± 2.7‡	149 ± 2.3	134 ± 7.0
Diastolic BP (mm/Hg)						
Initial	100 ± 0.9	104 ± 1.7	102 ± 1.5	100 ± 1.0	103 ± 1.5	102 ± 2.1
Final	85 ± 1.6‡	104 ± 2.3	95 ± 4.6	84 ± 2.0‡	101 ± 1.9	92 ± 5.2
Drug dose (mg/day)	280 ± 18	320 ± 15	220 ± 20	18 ± 2.2	32 ± 2.3	14 ± 2.8

*p = 0.02, †p = 0.002, ‡p = <0.0001, initial versus final treatment. Unless otherwise indicated, data are presented as mean value ± SEM. BP = blood pressure; NR = nonresponders; R = responders; W = withdrawn.

lisinopril-treated responders ($p < 0.0001$). There was no change in either systolic or diastolic pressure in diltiazem-treated nonresponders (Fig. 2). There was a modest but not significant decrease in systolic pressure (160 to 149 mm Hg) in lisinopril-treated nonresponders. There was no difference in the time to attain blood pressure control in responders in either treatment group (diltiazem 3.6 months, lisinopril 3.7 months). Patients in the nonresponder group participated for an average of 4.2 months (diltiazem 3.4 months, lisinopril 5.1 months) as dose titration continued to the maximal dose of the respective drug.

Serum creatinine. There was a significant increase in serum creatinine in the diltiazem-treated responders (1.36 to 1.54 mg/dl, $p = 0.02$) and the lisinopril-treated nonresponders (1.40 to 1.68 mg/dl, $p = 0.002$).

Cyclosporine levels. Each institution used the cyclosporine assay available through its respective laboratory. Cyclosporine trough levels were therefore analyzed by grouping patients in whom the same assay was used. Table 3 shows the available data including the type of assay used, as well as baseline and posttreatment cyclosporine levels in both treatment groups. Except for seven diltiazem-treated patients in whom the

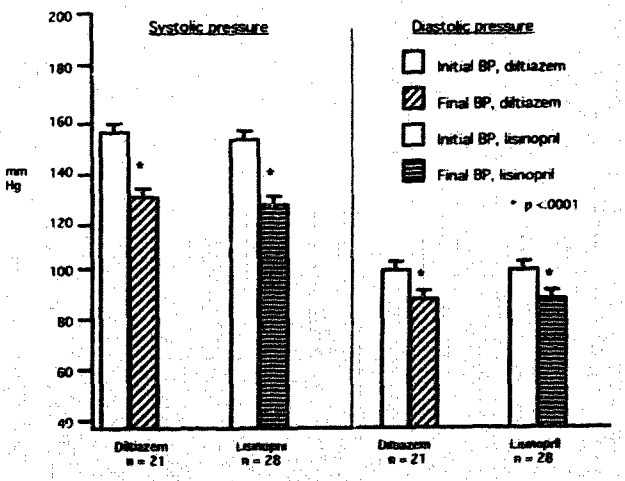

Figure 1. Blood pressure (BP) results in responders to diltiazem or lisinopril therapy.

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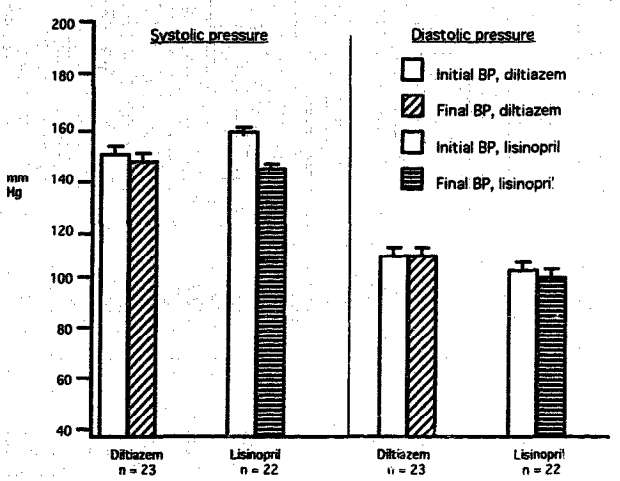

Figure 2. Blood pressure (BP) results in nonresponders to diltiazem or lisinopril therapy.

nonspecific radioimmunoassay was used, the cyclosporine level was lower at the end of the study than at baseline in both groups. This decrease may reflect the clinical practice of decreasing the target cyclosporine level over time.

Electrocardiography. A baseline ECG was performed in all patients. Serial ECGs were obtained after initiation of therapy or an increase in dose only in the diltiazem-treated group. There were no occurrences of second-degree or high grade AV block or symptomatic bradycardia in this group.

Adverse events. In the 55 patients treated with diltiazem, 18 adverse events were reported. In this group, the most common side effect was edema (five patients). Eleven patients were withdrawn from the study because of adverse events, not all of which were considered drug-related. There were two deaths. One patient died from pneumonia; the cause of death in the other patient is unknown but is not believed to be related to diltiazem. In the 61 patients treated with lisinopril, 17 adverse events were reported. In this group, the most common side effect was hypotension (three patients). Eleven patients were withdrawn because of adverse events and there were no deaths. As with the diltiazem group, not all adverse events were considered drug-related. Table 4 lists the adverse events in both groups and indicates which events were considered drug-related and which resulted in withdrawal from the study. All drug-related events resolved with discontinuation of the drug.

Table 3. Cyclosporine Trough Levels

Assay	Pretreatment		Posttreatment		Δ		p Value*
	No.	ng/ml	No.	ng/ml	No.	ng/ml	
RIA, specific							
Diltiazem	13	430 ± 38	11	340 ± 64	11	80 ± 64	0.3
Lisinopril	9	400 ± 83	13	280 ± 37	6	180 ± 89	0.10
p value*		0.7		0.4		0.4	
RIA, nonspecific							
Diltiazem	7	240 ± 38	5	360 ± 48	5	−90 ± 31†	0.05
Lisinopril	12	340 ± 69	10	310 ± 60	10	70 ± 68	0.3
p value*		0.3		0.6		0.14	
HPLC							
Diltiazem	14	260 ± 22	13	200 ± 28	13	60 ± 27	0.04
Lisinopril	15	200 ± 30	18	190 ± 23	13	30 ± 26	0.3
p value*		0.15		0.7		0.4	
Other							
Diltiazem	18	330 ± 41	18	230 ± 37	17	90 ± 35	0.01
Lisinopril	21	290 ± 37	18	200 ± 19	18	70 ± 26	0.01
p value		0.5		0.5		0.6	

*Change (Δ) in cyclosporine levels at baseline and after treatment. Negative value indicates an increase in level from pretreatment to posttreatment. Data are presented as mean value ± SEM. HPLC = high performance liquid chromatography; RIA = radioimmunoassay.

Table 4. Adverse Events

Adverse Event	Diltiazem (n = 55)	Lisinopril (n = 61)
Hypotension	2 (1) [1]	5 (4) [2]
Edema	5 (5) [2]	
Patient request	1 (0) [1]	3 (3) [2]
Increase in serum creatinine	1 (1) [1]	2 (2) [2]
Headache	1 (1) [1]	1 (1) [1]
Hyperkalemia		2 (2) [1]
Tremor	2 (2) [0]	
Hypertension	2 (0) [1]	
Death	2 (0) [2]	
Allergic reaction	1 (1) [1]	
Elevated alkaline phosphatase	1 (0) [1]	
Cough		1 (1) [1]
Ageusia		1 (1) [1]
Fracture femoral neck		1 (0) [1]

Numbers in parentheses indicate the number of patients whose adverse event was drug related; the numbers in brackets indicate the number of patients who were withdrawn from the study because of the adverse event.

Discussion

Compared with essential hypertension, hypertension after heart transplantation is characterized by features such as onset within days to weeks of transplantation, lack of normal nocturnal decrease in blood pressure and the effect of denervation on the left ventricular response to high systemic vascular resistance (5,6). Potential etiologic factors are multiple and include treatment with cyclosporine, obesity, sympathetic neural activation, effects of the renin-angiotensin-aldosterone system, volume expansion, renal dysfunction and, possibly, a cyclosporine-induced alteration of vascular response to endothelin (7–12).

Main findings of this study. This study has shown that short-term control of hypertension during the 1st year after heart transplantation can be achieved by monotherapy with long-acting diltiazem in 38% of patients and with lisinopril in 46% of patients. There was no difference in the efficacy of the two drugs or in the number of patients in each group withdrawn from the study because of adverse events. The treatment sample sizes were sufficiently large to have a power of 80% to detect a difference in success rate of 19% at the 0.10 level of significance.

Serum creatinine showed a statistically but not clinically significant increase in two groups: diltiazem-treated responders and lisinopril-treated nonresponders. Drug-related adverse events were minor and resolved with discontinuation of the respective drug. There were no differences in baseline characteristics between responders and nonresponders from which to predict response to either drug.

Comparison with previous treatment studies. Studies of various treatments for hypertension after heart transplantation have included careful reduction of cyclosporine dose (13), steroid-free maintenance immunosuppression and antihypertensive therapy. Two studies (14,15) have shown a greater incidence of hypertension in patients who continue to receive maintenance steroid therapy than in those who are on a steroid-free protocol. Another study (16) evaluated the effects of a low versus a high sodium diet in 12 patients after heart transplantation. Systolic blood pressure was significantly lower in the low sodium group, and the increase in both plasma renin activity and plasma atrial natriuretic peptide was blunted in these patients. In a retrospective study of 50 patients with a thoracic organ transplant (17), 45 of which were heart transplants, patients received either prazosin or nifedipine and had satisfactory blood pressure control with either drug. Creatinine clearance was better preserved in the nifedipine-treated group, indicating a possible nephroprotective effect of this calcium channel blocking agent. In a small prospective study of nine patients (18), treatment with enalapril and diuretic agents was started shortly after transplantation for treatment of hypertension. With an average dose of 11 mg of enalapril daily, in combination with an average dose of 62 mg of furosemide daily, adequate blood pressure control was obtained, and the serum creatinine level did not rise during the follow-up period of up to 2 years.

The effects of omega-3 fatty acids on control of posttransplant hypertension was also examined in a randomized trial of 20 heart transplant recipients (19). Results in this trial showed a 15% decrease in mean arterial pressure and a 32% reduction in systemic vascular resistance.

In a 1-month double-blind crossover trial of amlodipine or lisinopril in the treatment of hypertension in cyclosporine-treated patients with a renal transplant (20), amlodipine was found to be more effective than lisinopril in controlling hypertension. It was also associated with a consistent increase in glomerular filtration rate and effective renal plasma flow.

Study limitations. Although this study is the first collaborative, randomized, prospective multicenter trial of the treatment of hypertension in patients after heart transplantation, and has a larger number of patients than previously reported trials, certain limitations should be mentioned. 1) The trial was designed only to determine short-term efficacy and safety of diltiazem or lisinopril in the treatment of hypertension during the 1st year after heart transplantation. 2) The trial did not examine the effects of either a diuretic agent used on an as needed basis for edema or a second antihypertensive drug on blood pressure control. 3) Possible sequelae of hypertension in each treatment group and drug effects on these sequelae were not studied. 4) Cyclosporine assays were performed in each institution without the benefit of a central laboratory. Uniformity in cyclosporine assays would have improved the analysis of changes in the cyclosporine levels, particularly with regard to the diltiazem-treated patients.

Implications of the study. Our data show that either diltiazem or lisinopril used as titrated monotherapy achieves blood pressure control in <50% of patients with hypertension after heart transplantation. This finding reflects the clinical experience in this patient group of the frequent need to use more than one drug to achieve blood pressure control. Given the

different pharmacologic effects of each drug—namely, vasodilation by calcium channel antagonism or inhibition of the renin-angiotensin-aldosterone system by angiotensin-converting enzyme inhibition—our results suggest that the underlying pathophysiologic mechanisms can be altered by different approaches to therapy. In view of the long-term sequelae of posttransplant hypertension, further study of the underlying mechanisms, efficacy of selected drugs and the long-term effects of hypertension in these patients is needed.

Appendix

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*Participating centers are listed in alphabetical order with principal investigators†, co-investigators and coordinators.

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